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HODGKIN'S DISEASE

WITH SPECIAL REFERENCE TO ITS DIFFERENTIATION FROM OTHER DISEASES OF LYMPH NODES

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The pathologist is constantly confronted with the problem of making an accurate diagnosis of a disease from lymph nodes submitted to him for examination. The majority of the nodes are the material of biopsies on which the clinical interpretation of the diseases presented largely depends. It is of great importance to distinguish primary diseases from benign inflammatory lesions, and it is highly desirable to divide the various primary diseases as far as possible. In this paper an effort is made to show that Hodgkin's disease is a specific histologic entity and to differentiate it from other diseases of lymph nodes.

Pathologic conditions in lymph nodes may be divided into two groups: those which are secondary to disease elsewhere in the body and those in which lymphoid tissue is the structure primarily involved. The first group includes simple hyperplasia, acute and chronic inflammation and metastatic tumor infiltration. The second group includes the leukemias and reticulo-endotheliosis, the various types of lymphosarcoma, reticulo-endothelial sarcoma, endothelioma and Hodgkin's disease.

The first group ordinarily gives little difficulty in diagnosis, although a marked hyperplasia in a node may bear a close resemblance to some primary disease in the early stages of its development. The second group has always given difficulty from the time it was first realized that all noninflammatory lymphoid enlargements are not the same.

MATERIAL

The material used in this study was obtained from the pathologic laboratory of the University of Minnesota. It represented (1) thirty-eight cases of Hodgkin's disease complete with autopsy material and clinical history; (2) fifty cases of Hodgkin's disease diagnosed from lymph nodes removed surgically; (3) a group of cases in which the lymph nodes showed diseases other than Hodgkin's disease, including twenty-seven cases in which autopsy was performed (lymphatic leukemia, five; myelogenous leukemia, five; aleukemia, five; reticulo-endotheliosis, one; lymphosarcoma, five; reticulum cell sarcoma, five; endothelioma, one) and twenty-five cases in which surgical specimens were available (lymphatic leukemia, five;

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aleukemia, five; endothelioma, five; lymphosarcoma, five; reticulum cell sarcoma, five), and (4) forty cases in which surgical specimens of lymph nodes showed secondary diseases (simple hyperplasia, ten; nonspecific inflammation, acute and chronic, ten; tuberculosis, ten; tumor metastases, ten). There was a large number of cases in which lymph nodes were examined which have not been included in these special groups.

The majority of the specimens were fixed in solution of formaldehyde. In many cases tissue was also fixed in special solutions, such as Zenker's fluid, Helly's [1] fluid, alcohol, and solution of formaldehyde saturated with corrosive mercuric chloride. For general histologic structure, staining with hematoxylin-eosin was found satisfactory. Perdrau's modification of Bielschowsky's silver stain was also used on the majority of the surgical specimens. Goodpasture's carbolfuchsin-methylene blue stain, Mann's eosin-methylene blue stain, Pappenheim's methyl green-pyronine stain, Giemsa's stain and Dominici's stain were used for the determination of special cell characteristics.

DISEASES SECONDARY IN LYMPH NODES

When a lymph node is irritated by any stimulus its response is a hyperplasia of either reticulum cells or lymphocytes or both. Lymphocytes may multiply and become densely packed. The sinuses may be narrowed but are never obliterated. When there is a normal number of reticulum cells, the proportion of these cells to lymphocytes may be decreased. At times a marked increase in the size and the number of germinal centers is the outstanding feature. Most frequently there is an increase in the number of cells lining the sinuses. These cells may become free polyblasts or they may remain in a syncytial network filling the open spaces. If they remain fixed, the appearance is sometimes called "sinus catarrh." A hyperplasia of either reticulum cells or lymphocytes may occur as a preliminary stage of any primary disease of lymph nodes.

Acute inflammation showing hyperplasia plus the presence of pus cells often occurs when a node drains an infected area. Inflammation, either acute or chronic, shows no abnormal type of cell developing in the node. There is an infiltration from the blood stream of granulocytes, and both reticulum cells and lymphocytes may proliferate. Polyblasts and fibroblasts may be formed, but all development is along normal lines and there is no disturbance in the usual process of cell formation. The only exception to this is in patients suffering from certain severe infections in whom bacteria enter the blood stream, as in those with subacute bacterial endocarditis, or in very young children who are critically ill. Occasionally this stimulus is enough to produce a disturbance which simulates a leukemia, but the process in the nodes is rarely marked enough to confuse the diagnosis.

1. Helly's fluid was the stock solution made up as follows: potassium bichromate, 5 Gm.; mercuric chloride, 12 Gm.; water, 200 cc. At the time of use, 5 cc. of solution of formaldehyde is added to 95 cc. of stock solution. Tissue is immersed for five hours and then washed in running water for twenty-four hours.

A metastatic tumor appearing in a node may act as an irritant and produce hyperplasia in the part not destroyed by tumor tissue. Fibrocytes develop from reticulum cells and produce the collagenous tissue often seen in such lymph nodes.

The outstanding characteristic in hyperplasia and inflammation is the lack of obliteration of the general structure of the node. The sinuses and follicles and their general relationships are preserved except where destroyed by tumor cells or a necrosing inflammation. In differentiating between this group and the diseases primary in lymph nodes this is an important point to consider. The cells all arise in the way in which they are normally produced.

DISEASES PRIMARY IN LYMPH NODES

Hodgkin's Disease.[1a]—The typical microscopic picture of a lymph node involved in Hodgkin's disease includes a diffuse proliferation of reticulo-endothelial cells, an increase in collagenous and reticulum fibers, a diffuse sprinkling of plasma cells and eosinophils and the presence of cells designated as "Dorothy Reed cells" or "Paltauf-Sternberg cells." The latter cells are the only ones not found in other diseases of lymph nodes. They were described by Reed [2] as large cells with irregular vesicular nuclei, usually multiple, with a prominent chromatin network, and often containing nucleoli. They were described by Sternberg [3] as cells with one or more nuclei, much intensely staining chromatin and abundant cytoplasm. Both Reed and Sternberg believed them to be modified reticulum cells. Subsequent investigators have frequently recognized two types of cells, stating that one or the other is predominant in any one case. Occasionally any large reticulum cell is called a Dorothy Reed cell. Investigators vary in their opinion as to whether the presence of these cells is necessary for the diagnosis of Hodgkin's disease.

One of the chief interests in this study has been to determine whether there is a cell characteristic of Hodgkin's disease. The conclusion has been drawn that there is a specific cell found only in this condition and that in its absence the disease cannot be positively diagnosed. It can be traced from the reticulum through many forms. It has a much more variable appearance than is generally recognized, and is better designated "Hodgkin cell" than limited by the name of Reed or Sternberg. Many different fixatives and methods of staining were used, but the Dominici stain following fixation in solution of formaldehyde U. S. P. (1 : 10) saturated with corrosive mercuric chloride demonstrates the characteristics of these cells and differentiates them from other cells better than any other method.

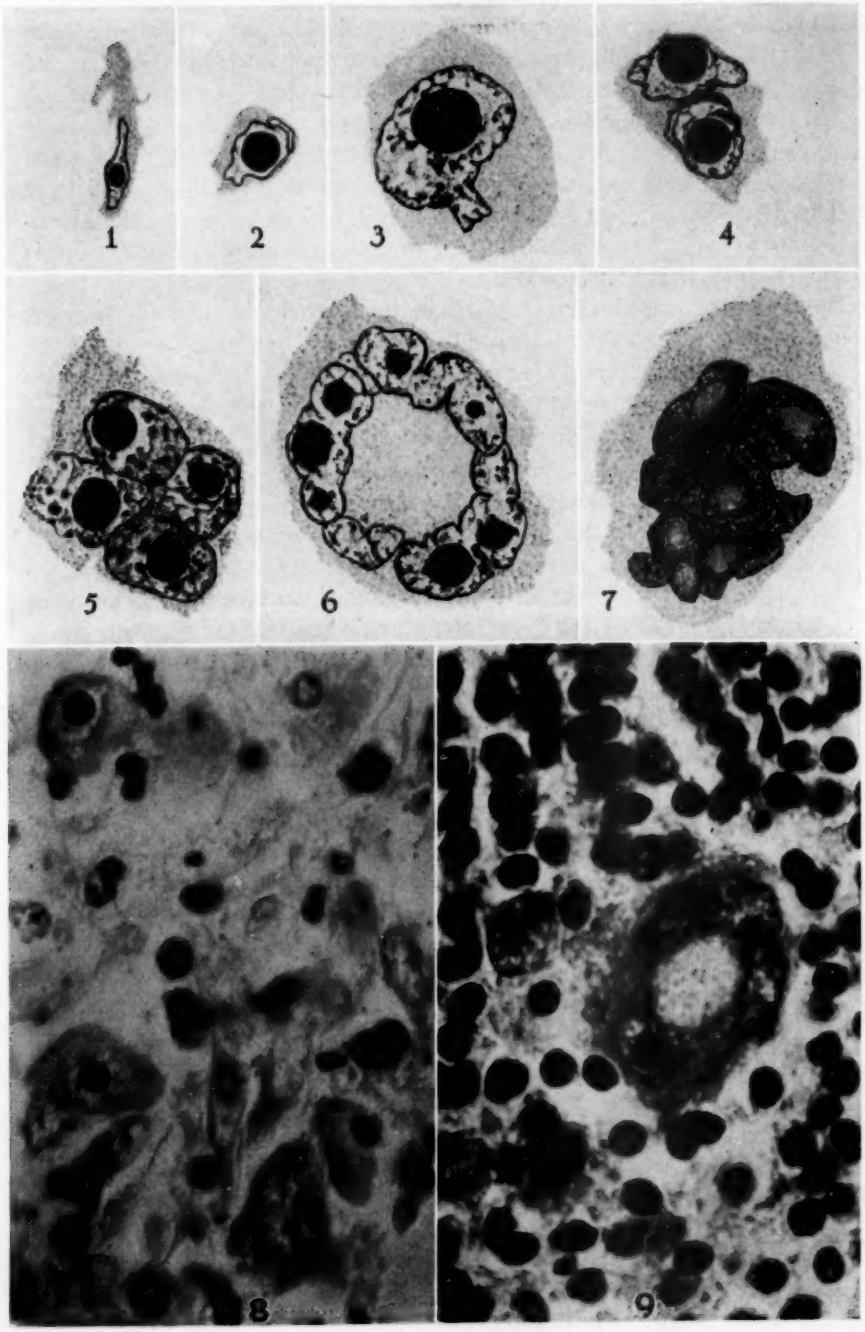
1a. Hodgkin, T.: Tr. Med.-Chir. Soc. Edinburgh **17**:68, 1832.
2. Reed, Dorothy: Bull. Johns Hopkins Hosp. **10**:142, 1902.
3. Sternberg, C.: Ztschr. f. Heilk. **19**:21, 1898.

The cells range in size from those no larger than a lymphocyte to those 35 or 40 microns in diameter. They may be round, oval or irregular in outline. The larger cells frequently have many irregular protoplasmic projections resembling pseudopodia. There is rarely a distinct cellular membrane, although when fully developed they are always free cells. Unless a stain is used which differentiates the cytoplasm of these cells from that of reticulum cells, they may appear to be part of the fixed syncytium. With many methods the cytoplasm gives a suggestion of being slightly granular, but with Dominici's stain after corrosive mercuric chloride fixation definite small light pink granules are demonstrated in a blue cytoplasm. The granules are very fine, and they may resemble a mass of pink cytoplasm surrounding the nucleus and extending almost to the periphery of the cell. When the cells are ruptured, however, the liberated pink granules are visible, disseminated over the surrounding areas. The only other cell whose cytoplasm has any similarity to that of the Hodgkin cell with this technic is the plasma cell. The region of the hof in the plasma cell may take a pink stain and the remainder of the cytoplasm a blue stain, but granules cannot be demonstrated. The area taking the pink stain is on only one side of the nucleus and is very small in relation to the blue cytoplasm. The nucleus of the plasma cell is also characteristic. The relation in Hodgkin's cell between the area composed of pink granules and that showing homogeneous blue cytoplasm varies. The granular area may practically fill the entire cell, or there may be only a very small area near the nucleus. Usually the entire cytoplasm is filled with granules, only a narrow rim of blue cytoplasm appearing at the edge. With Pappenheim's stain following fixation in either Zenker's fluid or a solution of formaldehyde saturated with corrosive mercuric chloride, very small deep pink granules are also visible. With this stain the cytoplasm is the same color as the granules.

The nucleus of the Hodgkin cell is extremely variable, depending on the degree of development from reticulo-endothelium. It may be a single round structure, often extremely wrinkled because of the shrinkage in fixation and no larger than a normal reticulo-endothelial nucleus. It usually becomes larger as the cell differentiates; the karyoplasm increases, and the chromatin appears as fine strands or granules scattered irregularly through the nucleus. The amount of chromatin in proportion to karyoplasm is so small that the nucleus is pale. The nucleus may become very large, measuring frequently from 15 to 18 microns or more. The cytoplasm increases at the same time so that the total diameter of the cell may be from 30 to 35 microns or even greater. At any stage of development indentation of the nucleus may occur. This may be slight or almost complete so that only a fine strand unites the two lobes. There may be development from two

into many lobes. Occasionally the lobes may become completely separated, producing a multinucleated cell, but the majority of the cells are polymorphonuclear rather than polynuclear. Because of the fineness of the connecting strands and the relatively large size of the lobes it is very difficult to see the connecting bands. From two to eight or ten lobes may be seen. They may be massed in the center of the cell (fig. *7*) or arranged in a wreathlike formation around the periphery (fig. 6). Mitotic figures are never seen in any stage beyond the mononucleated cell. The maximal size of the polymorphonuclear cells is rarely more than that reached by the giant mononucleated cells.

One of the most characteristic features of the nucleus is the presence of a very prominent nucleolus. Many authors have mentioned the occasional occurrence of a nucleolus, or stated that small irregular patches of massed chromatin were sometimes found, but the nucleoli have never been stressed as an important element. In all of the cases of Hodgkin's disease examined in this study they have been present. They are not found in all the cells, but this is probably due, in some instances at least, to the fact that large nuclei are not entirely included in a thin microscopic section. There is never more than one nucleolus to a single round nucleus or one to a lobe of a polymorphous nucleus. They are seen developing from minute indistinct nucleoli, growing gradually larger until they reach a diameter of as much as *7* microns. The usual size is from 3 to 4 microns. They are usually round or oval, rarely elongated or branched, dense, solid structures, sharply demarcated from the chromatin. Occasionally one or two minute vacuoles are present. They are usually metachromatic. With most stains they take a color in sharp contrast to the chromatin. In the polymorphous giant cells containing much deep-staining chromatin, the nucleoli are frequently almost obscured, but careful examination will usually reveal their presence. The nucleolus is found in any stage of nuclear change previously described: in the nucleus 5 or 6 microns in diameter, identical with a small reticulo-endothelial nucleus and still part of a fixed syncytium, in which the nucleolus may practically fill the entire space enclosed by the nuclear membrane (fig., *1*); in the nucleus of similar size belonging to the cell which has been isolated from the syncytium and surrounded by a definite narrow cytoplasmic zone (fig., *2*); in the giant nucleus of the large mononucleated cell (fig., *3*); in each lobe of the polymorphous nucleus (fig., *4* to *7*). It is sharply circumscribed and resembles a sphere suspended in the center of the nucleus. Occasionally it is found as a free isolated body, having been torn from the nucleus in preparation of the section. In the cell with only a small amount of chromatin, the chromatin is frequently found clumped in the center around the nucleolus and at the periphery of the nucleus with a relatively clear intermediate area.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EXPLANATION OF FIGURE

In *1* to *7* are reproduced camera lucida drawings (× 1,000) of Hodgkin cells:

1. Small fixed reticulo-endothelial cell already showing the characteristic nucleolus.

2. Small free reticulo-endothelial cell with the nucleolus almost filling the nuclear space.

3. Giant mononuclear cell of a type frequently found in Hodgkin's disease with the nucleolus containing a vacuole.

4. Cell containing two nuclei, each with a nucleolus.

5. Further multiplication of nuclei in a Hodgkin cell.

6. Giant cell frequently confused with a megakaryocyte. The polymorphous structure of the cell is well shown.

7. Giant cell containing much dark chromatin in which nucleoli are visible in microscopic examination only on very sharp focusing.

8. Photomicrograph of lymph node tissue showing Hodgkin's disease. Several typical mononuclear cells with large nucleoli may be seen.

9. Photomicrograph of lymph node tissue showing Hodgkin's disease. A characteristic giant cell may be seen.

Nucleoli are not present in every cell but are found in a majority of them and are the most characteristic feature of Hodgkin's disease. In the absence of the characteristic nucleolus, the Hodgkin cell, if mononuclear, cannot be distinguished from any large reticulum cell or, if polymorphonuclear, from the cells which occasionally occur in any severe inflammatory reaction, myelogenous leukemia or lymphosarcoma. Similar polymorphous cells without nucleoli were seen during this study in nodes from patients with, respectively, exfoliative dermatitis, myeloid metaplasia occurring in myelogenous leukemia, and lymphosarcoma. Small irregular nucleoli may be seen in many cells in many different conditions, but in no condition except Hodgkin's disease do they reach this immense size in cells of reticulo-endothelial origin.

Certain tumors, especially hypernephroma, squamous cell carcinoma and malignant melanoma, may be made up of cells containing prominent nucleoli. These nucleoli are about the same size as those found in the majority of Hodgkin cells, but they never attain the size which may be reached by those in Hodgkin cells. Except for the nucleolus the cellular structure of these tumors is different from that observed in Hodgkin's disease and it is rarely difficult, when the cells are in lymph nodes, to tell that they are neoplastic metastases. In malignant tumors the nucleoli are found consistently in cells of one type and never in cells showing such pleomorphism as do those of Hodgkin's disease.

The immense size of the nucleolus, especially in the small cell in which it almost fills the nucleus, suggests that it may be an intranuclear inclusion body similar to those described in virus diseases. The staining reaction is identical with that reported by Green [4] for the intranuclear inclusions of fox encephalitis. The nucleoli are found in only one type of tissue as is true of many inclusion bodies. The fact, however, that the nucleoli may be seen developing from small areas which are similar to the small nucleoli visible in many cells, and that it is impossible to demonstrate other, true nucleoli if one of these large intranuclear bodies is present, indicates that the intranuclear body is an integral part of the cell and not extraneous material introduced from without.

Downey's [5] technic for identification of megakaryocytes was followed in an attempt to determine whether Hodgkin cells were megakaryocytes, in spite of the fact that normal megakaryocytes do not have such prominent nucleoli. Corrosive mercuric chloride in solution of formaldehyde U. S. P. (1 : 10) used as a fixative followed by Dominici's stain failed to give evidence that these were megakaryocytes, but did show, as stated previously, that this is among the best methods of identifying Hodgkin cells.

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4. Green, R. B.; Katter, M. S.; Shillinger, J. E., and Hanson, K. B.: Am. J. Hyg. **18**:462, 1933.

5. Downey, H.: Anat. Rec. **9**:73, 1915; **11**:350, 1916-1917.

Hodgkin cells in a lymph node vary in number and location. In the early stages of the disease there may be (1) a normal histologic structure with small foci of Hodgkin cells in the follicles (2) hyperplasia of littoral cells with follicles normal except for small localized foci of Hodgkin cells, (3) generalized hyperplasia of reticulum cells of follicles and sinuses with a few scattered Hodgkin cells or (4) moderate hyperplasia of lymphocytes with narrowing of sinuses and isolated foci of Hodgkin cells. As the disease progresses, Hodgkin cells become diffuse throughout the node. They may remain few in number and be largely overshadowed by the other elements, or they may be so numerous as to be predominant. When they are round and polymorphonuclear, with much dark chromatin, they stand out prominently against the remainder of the tissue. The cells with hyperchromatic nuclei are never the only type of Hodgkin cells present. Associated with them are the more or less polymorphonuclear paler cells. When a large amount of fibrous tissue has developed, the cells frequently occur in small groups between the fibers. They are the last cells to be replaced by collagen. When the sinuses are still visible in a node they are frequently packed with all stages of developing Hodgkin cells, some even showing mitotic figures. There is rarely any evidence to show the origin of these cells from the lining of the sinuses in lymph nodes, although this is undoubtedly at least an occasional source for them. They can be seen originating from the reticulo-endothelium lining the sinusoids of the liver; the potentiality for cell development of reticulo-endothelium lining the sinuses of the lymph nodes is the same.

When large areas of Hodgkin cells are present in which the mononuclear type predominates, the lesion may be confused with lymphosarcoma. Lymphosarcoma, however, shows an almost uniform development of only one type of cell in any one case, while in Hodgkin's disease there is always some variety in the cells present; Hodgkin cells are never found to the exclusion of all other cells. The nucleoli in lymphosarcoma are never such large, sharply isolated structures; the cytoplasm is less in amount, and multinucleated cells are rare.

In Hodgkin's disease the reticulo-endothelium shows a diffuse proliferation, particularly of the cellular syncytium forming the groundwork of the follicles. Any irritant produces proliferation of sinus cells but under practically no other circumstances than Hodgkin's disease does the follicular reticulum proliferate to such an extent. As it progressively increases, the sinuses are encroached on and almost completely obliterated. Many of the cells remain as simple reticulum and give a syncytial cytoplasmic background for the other superimposed elements. Some acquire the granular deeper-staining cytoplasm and giant nucleoli of Hodgkin cells. Some develop into fibroblasts and fibrocytes. Although

Pullinger's [6] technic (Mann's long eosin-methylene blue stain) was used in many cases, no evidence could be found to corroborate his theory that eosinophils develop from reticulum.

The reticulum fibers are invariably increased in Hodgkin's disease. The most satisfactory stain to demonstrate this is Perdrau's modification of Bielschowsky's silver impregnation. In some cases the increase in fibers is found so evenly distributed throughout the node that there is no evidence of the original location of the sinuses, but in most cases the newly formed fibrous tissue is more dense at the periphery of the follicles and in the region of the blood vessels. The reticulum fibers gradually develop into collagenous fibers. Collagenous fibers are usually first formed in these same areas, i. e., the periphery of follicles and around blood vessels. The reticulum fibers vary from extremely fine, hairlike branches to heavier trunks formed by the coalescence of the finer branches. They are present everywhere between the cells except where there are solid areas of Hodgkin cells. Hodgkin cells are usually seen as free, completely isolated cells with no relation to reticulum fibers.

This increase in reticulum fibers is an aid in differentiating Hodgkin's disease from lymphosarcoma and leukemia. In neither of the two latter conditions is there much increase; in fact, because of the increase in free cells, the fibers seem even fewer than normal. There is rarely a complete absence of fibers except among the syncytial cells in endothelioma. Here the pavement-like areas of cells have no fibers within them, but there are fine reticulum fibers scattered throughout the rest of the node. In lymphadenitis there may be a moderate increase of reticulum fibers but not to the extent that is usual in Hodgkin's disease. The majority of collagenous fibers present in the healing stages of an inflammation in lymph nodes come directly from fibroblasts instead of from preliminary reticulum fibers.

The fibroblasts in Hodgkin's disease are practically always increased, but in varying degree. In an early stage there are many young cells with plump vesicular nuclei only slightly modified from reticuloendothelium. When in large numbers with a few other cells intermingled they may resemble slightly the epithelioid cells of tuberculosis. As the condition becomes more advanced they become more mature and produce collagenous fibers. The collagenous fibers increase at the expense of the other elements so that the cells between them become fewer and fewer. They may become so numerous that they obliterate all other structures and leave a node composed entirely of collagenous material. The last cells to disappear in this fibrosis are the Hodgkin cells, and occasionally one may see collagenous fibers and practically no

6. Pullinger, B. D.: Histology and Histogenesis of Lymphadenoma, in Horder, Thomas, and others: Rose Research on Lymphadenoma, Bristol, John Wright & Sons, Ltd., 1932, p. 117.

other cells but these making up large areas. After roentgen treatment the nodes are largely replaced by connective tissue in a similar fashion.

Irregular areas of collagenous material may be seen occasionally in leukemia and rarely in lymphosarcoma, but there is never a generalized increase in connective tissue. A very few cells may apparently form large masses of collagen. These areas must not be considered a reason for calling a leukemic condition of the node Hodgkin's disease.

Lymphocytes of all sizes are present in Hodgkin's disease. In an early stage they may be increased in number, but as soon as the reticulum shows any marked degree of proliferation, they become fewer. As the disease progresses, they fail to multiply in normal numbers and become reduced both actually and relatively. Single islands of lymphocytes may remain for a long time, being small areas which have escaped involvement in Hodgkin's disease. In a node showing complete involvement only a few scattered small lymphocytes remain.

Germinal centers are absent from the onset. The belief of Reed, Symmers and Longcope that a lymphocytic hyperplasia signalized the onset of Hodgkin's disease has led to most of the confusion in differentiating it from leukemia. In very early cases of either Hodgkin's disease or leukemia it is possible that the only abnormality in the lymph nodes may be a simple increase in the number of lymphocytes. The hyperplasia in this early stage is not different from that caused by any irritation, and neither Hodgkin's disease nor leukemia can be diagnosed. A lymph node from a patient with more advanced leukemia shows obliteration of the normal structure by lymphoid cells and its condition bears little resemblance to the simple hyperplasia possible very early in Hodgkin's disease and none to the changes seen when the disease is well developed.

Eosinophils are present in most cases but in varying numbers. With a stain that brings out the granules in the cytoplasm (Dominici's or eosin-methylene blue) a few will be seen in every case. Frequently they are the most numerous cells present in localized areas in the node. They are usually most numerous in the areas containing the most reticulum fibers, which are around the blood vessels or in the region of the original site of the sinuses. In the material concerned here there is no evidence of local origin. They are mature cells. They are rarely present in leukemia or lymphosarcoma.

Plasma cells are present almost as constantly as eosinophils and are frequently as numerous. Their point of origin cannot be demonstrated, but since they are usually derived from lymphocytes and their presence in lymph nodes is normal, the lymphocytes are their probable source. The best stains to demonstrate their presence are Dominici's stain or Pappenheim's methyl green-pyronine. Plasma cells are rare in leukemia or lymphosarcoma.

Necrosis is frequently present in either large or small areas. Small patches in the midst of masses of collagenous fibers are most common. The necrotic area has a very indefinite margin, fading gradually into the surrounding tissue, and is never surrounded by a zone of reaction. There is rarely complete destruction of all tissue. The blood vessels in the area remain intact, and the general structure has the "burned over" quality frequently found in syphilis; rarely is there the complete necrosis of tuberculosis. These areas gradually enlarge and may rarely, in time, involve the whole node.

Individual necrotic cells are occasionally seen, although not as frequently as in leukemia. Dark crescentic masses may be present on one or two sides of small acidophilic globules, representing nuclear remains. They are the same as the phagocytosed material called "Flemming's stainable bodies" which are found in large reticulo-endothelial cells. They are much more frequent in leukemia than in Hodgkin's disease.

When Hodgkin's disease is advanced, the normal structure of the node is almost constantly destroyed. As noted before, there may be localized areas of involvement in an otherwise normal node, but when the disease is well developed the increase in follicular reticulum cells is so great that it obliterates the sinuses and gives a uniform appearance to the entire node. The node frequently appears as a mass of tissue having a uniform structure throughout, with no sign of follicle, germinal center or sinus. Occasionally some of the larger sinuses in the medulla are visible even in advanced cases, but if the sinuses throughout the node are well defined, it is a point against the diagnosis of Hodgkin's disease. Occasionally isolated sinuses are visible which are filled with Hodgkin cells. An obliteration of normal structure also occurs in leukemia and lymphosarcoma.

The capsule of the node forms only a temporary limit to the tissue proliferating within. The wall becomes easily infiltrated, and very frequently the surrounding tissue is invaded.

Sarcoma.—According to Kundrat's[7] definition, only those conditions may be called "sarcoma of lymphoid origin" in which there is a known primary tumor of lymphoid tissue from which definite metastases can be traced. This has led to an almost exclusive use of this term for cases in which large tumors of the pharynx, intestinal tract, mediastinum, retroperitoneal region or mesentery are shown with little generalized involvement of the lymph nodes. There are many cases, however, in which a more or less widespread lymphadenopathy is present and in which the involved areas show a histologic structure identical with that seen in the localized tumors. It has been the custom of some pathologists to call such identical lymph node involvements "lymphosarcoma"

7. Kundrat: Wien. klin. Wchnschr. **6**:234, 1893.

in the cases in which enlargement is localized and "cellular Hodgkin's disease" in those in which the adenopathy is generalized, thus making the differential diagnosis on history alone. These conditions bear no resemblance histologically to what is recognized as typical Hodgkin's disease and the involved nodes do not contain Hodgkin cells. If one is ever to realize what Hodgkin's disease actually is one must adhere to what is cytologically characteristic. A large part of the cases of so-called cellular Hodgkin's disease should be removed and placed with the cases of sarcoma. If desired, a distinction may be made by designating the localized tumors as primary lymphosarcoma of certain organs and those with widespread adenopathy as generalized lymphosarcoma.

The term "lymphosarcoma" is generally used to designate a sarcoma arising from any cellular element in lymphoid tissue. More recently there has been a tendency to restrict it to tumors composed of free cells and to use "reticulo-endothelial sarcoma" if the majority of the cells remain fixed.

Accurately used, "reticulo-endothelial sarcoma" should include both the tumors containing cells resembling reticulum (reticulum cell sarcoma) and those developing along the line of littoral cells, the endotheliomas. The term "endothelioma" has become so firmly entrenched, however, that at present the tendency is to leave the tumors thus designated as a separate group and to use "reticulo-endothelial sarcoma" ("retithelioma") and "reticulum cell sarcoma" ("reticuloma") interchangeably.

Histologically lymphosarcoma shows obliteration of the normal structure by the proliferation of a single type of large free mononucleated cells. This type has a scanty amount of basophilic cytoplasm and a large vesicular nucleus, which is frequently much distorted. The chromatin is finely granular or arranged in a network, and is often smaller in amount than in the normal lymphocyte. The cells rarely have nucleoli. Occasionally a cell with two or three nuclei may be seen. The cells are more or less closely packed and are irregular in outline because of this close juxtaposition. They are the largest free cells found in lymph nodes in conditions other than Hodgkin's disease. They frequently measure 10 microns and are distinctly larger than those usually found in leukemia. Mitotic figures are often present in great numbers. Even though there is rapid cell proliferation in leukemia, such frequent mitosis is rarely visible. The framework of the node is scarcely visible because of the number of free cells. There is rarely much proliferation of normal reticulum cells but, as in any tumor, connective tissue cells may develop, and there are occasionally small areas of collagenous fibers. Unless roentgen treatment has been given, there is rarely marked fibrosis of a node. Necrosis is extremely uncommon. Eosinophils, plasma cells and normal lymphocytes are almost constantly

absent. As in Hodgkin's disease, there may be a small focus of tumor tissue in an otherwise normal node. It may be differentiated from Hodgkin's disease by the almost exclusive preponderance of one type of cell and the consequent absence of the pleomorphism of Hodgkin's disease. Hodgkin cells are absent. Silver impregnation shows only a few reticulum fibers in any part of the node.

A few investigators recognize a small cell lymphosarcoma or lymphocytoma with the same characteristics as have been described, except that the cell type is a mature lymphocyte. It is apparently this condition which is said to develop into leukemia, and it probably always represents leukemia in an aleukemic phase. Histologically it cannot be differentiated from leukemia. If this condition is placed with the sarcomas, sarcoma in certain cases is identical with leukemia, and this only adds to the confusion of diagnosis. The diagnosis of small cell lymphosarcoma should be eliminated in the consideration of lymph node enlargements and all such enlargements considered as aleukemia.

The two types of reticulo-endothelial sarcoma are (*a*) that in which the entire node is composed of tumor tissue in which a few cells are free while the majority are still a part of a loose irregular syncytial background and (*b*) that in which the cells are in relatively solid masses with cell boundaries not distinguishable. In the first group are the tumors containing cells similar to reticulum cells, except that they are larger and frequently more hyperchromatic. They may resemble the cells of lymphosarcoma closely, except that they retain at least a part of their syncytial arrangement. They are called "reticulum cell sarcoma" by Ewing [8] and "retithelial sarcoma" by Roulet.[9] In the second group of tumors, in which solid masses of cells predominate, there may be a considerable amount of normal or hyperplastic node in areas not involved by the masses of tumor cells. The nucleus of the tumor cell is usually large and vesicular with a heavy nuclear membrane. It contains only a small amount of chromatin arranged in the network characteristic of most reticulo-endothelial cells. It frequently has a small but rather prominent nucleolus. The cytoplasm varies in amount. Usually cell boundaries are indistinguishable, and the nuclei appear to be set in a solid sheet of cytoplasm. This is the endothelioma of Ewing.[10] In this group very anaplastic metastatic squamous cell carcinoma may be erroneously included. This is composed of solid sheets of cells and may resemble endothelioma very closely. This tumor is called "lymphoepithelioma." The primary growth is usually situated in the pharynx and is readily overlooked in the earlier stages of the disease.

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8. Ewing, James: J. M. Research **28**:1, 1913.

9. Roulet, F.: Virchows Arch. f. path. Anat. **277**:15, 1930; **286**:702, 1932.

10. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

Among the operative specimens studied, which in general represent less advanced cases than those from autopsy material, there are many nodes which show a hyperplasia of follicular reticulum cells so marked as to obliterate the sinuses, but with many lymphocytes still present. It is difficult to know whether the condition in these nodes will develop into Hodgkin's disease or progress to the formation of solid reticulo-endothelial sarcoma of the endothelial type. In the absence of Hodgkin cells neither diagnosis can be made with certainty.

In the syncytial reticulo-endothelial sarcoma silver impregnation shows fine reticular fibers arranged in such a way that the cells seem to cling irregularly along the fibers. In the endotheliomatous type there are almost no fibers in the solid areas of tumor tissue.

Growths of the group of sarcomas may produce lesions in any organ, but they do so with less frequency than does Hodgkin's disease. In metastases they show a greater local destructive power. The cell structure in metastases is similar to that in the lymph nodes.

Myeloid sarcoma is reported by several authors, but there are no conditions which can be so diagnosed in the material on which the present study is based. It has been recognized as arising especially from bone, although other locations have been described. It contains developing myeloid cells and cannot be differentiated histologically, especially in the metastases to nodes, from simple myeloid metaplasia. It is believed that it represents a hemocytoblastic development from primitive mesenchyme but one differentiating along myeloid instead of lymphoid lines. This is a theoretical possibility, but evidence for it is rarely observed.

The entire group of malignant growths arising from lymphoid tissue have the cell of the primitive mesenchyme as the parent cell. Typically the malignant cells show a slight development along the line of normal growth, i. e., toward the hematic cells in lymphosarcoma and myeloid sarcoma, toward reticulum in reticulum cell sarcoma and toward littoral cells in endothelioma. Although the process usually remains constant, occasionally in different nodes of the same patient or at different periods of the disease, the structure may vary from cells that are free or fixed in one node to the opposite in another. This is because of the great potentiality of the parent cell for either line of development. A sharp distinction cannot always be made between the different types.

Leukemia.—Lymphatic leukemia shows in the lymph nodes a proliferation of cells approaching mature lymphocytes. A large number of these are not mature, as can be seen when they get into the blood stream, but, although they may be slightly larger than usual, they are distinctly smaller than those of the typical large cell lymphosarcoma. They are present in such numbers that practically no other cells are visible. The sinuses are obliterated, there are no germinal centers, and

demarcation of follicles is generally absent. The entire node is a solid mass of lymphocytes.

In rare cases a marked proliferation of reticulum cells occurs, giving on casual examination a suggestion of Hodgkin's disease. Careful study, however, reveals that the only line of differentiation occurring in the reticulum is into lymphocytes with an absence of anything resembling Hodgkin cells. This occurrence can be readily understood from the fact that in leukemia the cells may be derived from undifferentiated reticulum. They are ordinarily converted immediately into free cells, but at times there is proliferation with only part of the cells differentiating. When differentiation does occur it is entirely along lymphocytic lines. This type of case shows that reticulo-endothelial hyperplasia alone is an insufficient reason for diagnosing Hodgkin's disease.

Collagenous fibers may be present in leukemia as well as among the cells in Hodgkin's disease. In leukemia the collagen appears as small solid areas present irregularly throughout the node, much the same as in lymphosarcoma. It is never associated with marked fibrosis. Occasionally there are visible large reticulum cells full of small dark particles called "Flemming's stainable bodies," representing remnants of necrotic nuclei. These same remnants may occasionally be seen not yet taken up by phagocytes.

Myelogenous leukemia only infrequently involves peripheral lymph nodes. There is never the wild production of cells seen in lymphatic leukemia. The general structure of the node is usually fairly well maintained, and the principal involvement is that of the follicles, although a moderate proliferation of sinus reticulum such as is seen in any irritation may occur. In the follicles myeloid blood cells are produced from the local tissue, and granulocytes in all stages of maturity are present. Megakaryocytes are occasionally formed, and when this occurs there may be some confusion with Hodgkin's disease, the megakaryocytes being confused with Hodgkin cells. They do not contain typical nucleoli, however, and Hodgkin's disease never shows developing granulocytes. The involvement of organs outside of lymph nodes is the same as in lymphatic leukemia, except that it occurs where reticulum cells are especially prominent rather than where lymphocytes predominate. This is true especially in the spleen and the liver. The sinuses may contain many hemocytoblasts or developing granulocytes which have arisen from the littoral cells.

In the monocytic leukemia of Schilling [11] the most marked feature is a proliferation of the reticulum cells of follicles and sinuses. Some of these differentiate into monocytes, but many remain for a long time as reticulo-endothelial cells. The sinuses are rarely entirely obliterated

11. Schilling, Victor: Deutsche med. Wchnschr. **51**:261, 1925.

and usually may be seen packed with free cells, which are largely immature monocytes. Lymphocytes usually remain scattered throughout the node. A diffuse sprinkling of lymphocytes and immature monocytes among the markedly increased reticulo-endothelial cells is characteristic.

Occasionally the free reticulo-endothelial cells fail to differentiate into monocytes but get into the blood stream with an unchanged reticulo-endothelial nucleus. In cases in which this occurs the condition is called leukemic reticulo-endotheliosis. In tissue it is almost impossible to tell how much differentiation has occurred, so that in lymph nodes monocytic leukemia and leukemic reticulo-endotheliosis are almost identical.

An aleukemic state may be present in reticulo-endotheliosis as well as in myelogeneous and lymphatic leukemia, and it may be difficult to distinguish such a condition of the lymph nodes from Hodgkin's disease. In the one case of aleukemic reticulo-endotheliosis included in the records concerned here there was little difficulty in diagnosis, but in the literature there are reports of cases in which many eosinophils, giant cells of the Dorothy Reed type and fibrosis were observed. From the description it would seem as if many of these actually were cases of Hodgkin's disease. A thorough study of the free cells is the only way of proving that they are not. In the case just mentioned there was marked hyperplasia of reticulum, in places obliterating all other structures, but no differentiation in any part to anything resembling Hodgkin cells. All of the free cells, of which there were many, had reticulo-endothelial or polyblastic nuclei. There were no eosinophils. This is another illustration of the fact that reticulum cell hyperplasia alone is an insufficient basis for the diagnosis of Hodgkin's disease.

Naegeli [12] believes that monocytes are always derived from myeloid tissue and consequently that a leukemia in which immature monocytes are present is a subdivision of myelogenous leukemia and consequently a primary disturbance of bone marrow. Monocytes, however, have apparently two sources of origin, and two types of monocytic leukemia are recognized. In the group described by Naegeli there is little involvement of lymph nodes. If nodes are involved, it is because of a myeloid metaplasia as in myelogenous leukemia. The cells differ in developing toward monocytes instead of granulocytes.

COMMENT

In all diseases primary in lymph nodes, reticulo-endothelial tissue in any part of the body may be involved. These diseases involve primarily the undifferentiated reticulum cells, those cells which show no differen-

12. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

tiation into either sinus endothelium or phagocytic cells. These nonphagocytic reticulum cells may be considered either as resting cells of the reticulo-endothelial system or as an individual group known as primitive mesenchyme. Leukemia, lymphosarcoma and Hodgkin's disease may be called with equal accuracy "diseases of the reticulo-endothelial system" or "diseases of the primitive mesenchyme."

Leukemia is the result of a stimulation of the hematopoietic function of reticulum cells. There is an abnormal proliferation of reticulum cells, most of which develop rapidly into hemocytoblasts. An associated factor prevents normal maturation, so that many cells retain their primitive characteristics. Sarcoma of reticulo-endothelial tissue also results from abnormal proliferation of undifferentiated reticulum cells. In this case there is an entirely unsuccessful attempt to form mature cells, although there may be slight differentiation into hemocytoblasts, endothelium of sinuses or simple reticulum cells. The complete interference with normal development leads to the production of large masses of highly embryonic tissue. The attempted line of differentiation makes it possible to subdivide the group into lymphosarcoma (hemocytoblasts), endothelioma (sinus endothelium) and retithelioma (reticulum cells). Since the only difference between lymphosarcoma and retithelioma is in the degree of isolation of the cells, the two groups may at times be very similar.

In Hodgkin's disease there also is a proliferation of reticulum cells. There is neither interference with normal maturation of blood cells as in leukemia nor the formation of uniformly abnormal cells as in sarcoma. There is instead a development of reticulum cells along all lines normally followed, plus the formation of various types of abnormal cells. After proliferation the reticulum cells may remain as normal syncytial cells; they may become more completely fused and solidly packed and resemble endotheliomatous tissue; they may increase in size and develop more hyperchromatic nuclei while still retaining their syncytial character and resemble somewhat the cells of retithelioma; they may develop into the specific type of mononuclear or polymorphonuclear cells which are characteristic of Hodgkin's disease. In addition they may develop into normal hemocytoblasts, normal fixed or free phagocytes, or fibroblasts. In contrast to leukemia and lymphosarcoma there is always a protean type of cellular differentiation and not a limitation of development to one specific line. Hodgkin's disease is always characterized by pleomorphism of cells.

The microscopic appearance of Hodgkin's disease depends on the relative predominance of certain developmental tendencies, so that the histologic structure may vary widely. A definite diagnosis of Hodgkin's disease cannot be made without the presence of specific Hodgkin cells.

Hodgkin's disease of the endotheliomatous type should not be held identical with endothelioma, nor Hodgkin's disease of the cellular type with lymphosarcoma. Hodgkin's disease is a sufficiently complete diagnosis, but if one wishes to subdivide it according to the predominant cells, it may be stated that the type is endotheliomatous, reticular, cellular, sclerotic, etc. Such a diagnosis indicates that there is a variety of cells present, but that so far as one cell is predominant over the others it is the one which is included in the name. If there is no cellular variety and if Hodgkin cells are absent, Hodgkin's disease cannot be diagnosed. The condition must then be called "endothelioma," "lymphosarcoma," "reticulum cell hyperplasia," etc.

Hodgkin cells are occasionally absent from individual nodes, even when present in the majority. This is probably the main reason for the statement that endothelioma, lymphosarcoma, leukemia and Hodgkin's disease are present in the same patient or that one develops into another.

In typical cases, Hodgkin's disease, lymphosarcoma, retithelioma, endothelioma and leukemia have distinct characteristic microscopic appearances, but when the picture is not typical, Hodgkin's disease may, in localized areas, resemble any of the others. In a single node the presence of Hodgkin's cells and cellular pleomorphism make possible a definite diagnosis of Hodgkin's disease. The absence of these two requirements does not exclude the possibility of the node having been removed from a patient with Hodgkin's disease, but it does preclude making such a diagnosis.

Since all the diseases primary in lymph nodes may show reticulum cell proliferation, the presence of hyperplasia of these cells alone is insufficient evidence for making any specific diagnosis.

Klemperer [13] suggested the name "primary reticulum cell hyperplasia" for the condition of lymph nodes in which no abnormality is present except general loss of structure and proliferation of undifferentiated reticulum. This is a sufficiently complete diagnosis for the clinician and would prevent the accumulation of large numbers of so-called "atypical cases" of Hodgkin's disease, leukemia, etc. When a disease of a node is seen in this stage it is impossible to tell which of the diseases primary in lymphoid tissue it will eventually become. This diagnosis indicates that the condition belongs in the group of diseases primary in lymphoid tissue, and has an equally grave prognosis. It is of value in that it prevents the obscuring of present knowledge by a large accumulation of atypical cases of any of the aforementioned diseases.

13. Klemperer, Paul, in Contributions to Medical Science in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 655.

Typically in each disease primary in lymph nodes there is development along a specific line. In rare atypical cases the stimulus ordinarily producing a specific histologic change may lead to the formation of the type of tissue ordinarily produced by another cause and associated with another disease. The microscopic pictures of all diseases primary in lymph nodes may, in rare instances, in individual nodes, be identical, with the exception that Hodgkin's cells are never found except in Hodgkin's disease.

The conclusion is reached that Hodgkin's disease, the group of sarcoma arising from reticulo-endothelium, and the group of leukemia and aleukemia represent three distinct entities.

SUMMARY

Histologically the only specific feature of Hodgkin's disease is the Hodgkin cell.

Other features described as characteristic of Hodgkin's disease, such as loss of structure of the node, invasion of the capsule, hyperplasia of the reticulum cells, increase in the numbers of eosinophils and plasma cells, decrease in the number of lymphocytes, and fibrosis, are not specific for Hodgkin's disease either singly or collectively and occur in other diseases of lymph nodes.

Hodgkin cells are not present in every lymph node in Hodgkin's disease, but in their absence a positive diagnosis cannot be made.

CHANGES IN THE TEETH AND BONE IN CHRONIC FLUORIDE POISONING

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These experiments which were carried out on rats were started in an effort to ascertain the nature and character of the possible changes in bone that chronic fluoride intoxication may induce. It was considered likely that chronic fluoride intoxication may be the basis of clinical sclerosis of bone. Furthermore it was deemed desirable to correlate the changes in bone, if they occurred, with the changes in teeth appearing in such experiments.

REVIEW OF THE LITERATURE

The reports dealing with lesions in teeth show general agreement concerning the abnormalities resulting from fluoride poisoning. So far as the bones are concerned, those who have described changes were not in agreement as to their character. Some have reported osteoporosis, and others even the opposite, osteosclerosis. In 1891 Brandl and Tappeiner [1] fed 402.9 Gm. of sodium fluoride to a dog over a period of twenty-one months. This caused the bones to become whiter than normal and quite brittle. It was stated that fluoride crystals could be observed in the haversian canals and marrow spaces of these bones. Rost [2] described osteoplastic and osteoporotic changes in the bones of the dogs to which he fed sodium fluoride. Bony depositions were found at the sites of many of the muscle attachments. In 1925 McCollum, Simmons, Becker and Bunting,[3] while attempting to determine whether "bad" teeth were due to a deficiency in fluoride, found that the excessive ingestion of fluoride caused changes in the enamel of the incisors of rats. They also discovered that there was a secondary overgrowth of the upper incisors. The mandibles of their rats were described as osteoporotic. In the same year Schultz and Lamb [4] found similar changes in the incisors of rats when adequate amounts of sodium fluoride were added to the diet. Details of the gross and microscopic changes in

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1. Brandl, J., and Tappeiner, H.: Ztschr. f. Biol. **28**:518, 1891.

2. Rost, quoted by Moeller, P. F., and Gudjonsson, V.: Acta radiol. **13**:269, 1932.

3. McCollum, E. V.; Simmons, N.; Becker, J. E., and Bunting, R. W.: J. Biol. Chem. **63**:553, 1925.

4. Schultz, J. A., and Lamb, A. R.: Science **61**:93, 1925.

teeth of fluoride-fed rodents were reported by Bergara,[5] Chaneles,[6] Pachaly[7] and others.[8] Most of the reports stated that the incisors of rats (fed daily for over six weeks with 50 mg. or more of sodium fluoride per kilogram of body weight) showed stripings in the enamel. Longer periods of feeding for from ten to twelve weeks caused complete loss of the normal pigmentation of the enamel and secondary lengthening of the upper incisors. Most authors stated that chronic fluoride poisoning causes imperfect calcification of the dentin and enamel. Another effect noted was the irregular production of enamel substance.

In 1931 Smith, Lantz and Smith[9] proved experimentally that the fluoride present in the drinking water was the cause of the mottled enamel of their rats. Churchill,[10] in 1931, detected fluorine spectrographically in many of the waters in the United States, especially in parts of the country in which mottled enamel of the teeth was noted in the population. This finding confirmed the suspicion held by McKay[11] that the endemic occurrence of mottled enamel was to be related to the supply of drinking water.

So far as bones are concerned Bergara, Chaneles, Dittrich[12] and others reported the occurrence of generalized osteoporosis in their animals. Cristiani and Gautier[13] found the tibias of fluoride-fed guinea-pigs to be thickened but fragile. Bethke, Kick, Hill and Chase[14] observed no histologic changes in the bones of rats in fluoride poisoning. Dittrich[12] noted that the bones of his animals stained irregularly with alizarine and that porosity was present in the cortices. In swine and cattle changes in the teeth and bones were also noted after chronic fluoride intoxi-

5. Bergara, C.: Compt. rend. Soc. de biol. **97**:601, 1927; Rev. odontol. **9**:802, 1929.

6. Chaneles, J.: Compt. rend. Soc. de biol. **102**:860 and 863, 1929; Rev. Soc. argent. de biol. **5**:317, 336, 340, 352 and 376, 1929.

7. Pachaly, W.: Arch. f. exper. Path. u. Pharmakol. **166**:1, 1932.

8. DeEds, F.: Medicine **12**:1, 1933. McClure, F. J.: Physiol. Rev. **13**:277, 1933. Klein, H., and McCollum, E. V.: J. Dent. Research **13**:188, 1933. Armstrong, W. D.: ibid. **13**:223, 1933. Krasnow, F., and Serle, A.: ibid. **13**:239, 1933. Smith, M. C., and Leverton, R. M.: ibid. **13**:249, 1933. Phillips, P. H., and Lamb, A. R.: Arch. Path. **17**:169, 1934. Schour, I., and Smith, M. C.: Univ. Arizona Coll. Agric. Tech. Bull. 52, 1934.

9. Smith, M. C.; Lantz, E. M., and Smith, H. V.: Univ. Arizona Coll. Agric. Tech. Bull. 32, 1931.

10. Churchill, H. V.: Indust. & Engin. Chem. **23**:996, 1931.

11. McKay, F. S.: J. Am. Dent. A. **5**:721, 1918; **19**:1715, 1932; **20**:1137, 1933.

12. Dittrich, W.: Arch. f. exper. Path. u. Pharmakol. **168**:319, 1932.

13. Cristiani, H., and Gautier, R.: Compt. rend. Soc. de biol. **92**:139 and 946, 1925; **93**:911, 1925; **103**:554 and 556, 1930.

14. Bethke, R. M.; Kick, C. H.; Hill, T. J., and Chase, S. W.: J. Dent. Research **13**:473, 1933.

cation; Reed and Huffman [15] reported softening of the teeth and thicker and rougher mandibles in cattle. Bethke and his co-workers [14] found osteoplastic changes in the jaws of swine fed toxic quantities of fluoride. Microscopic sections of such bones demonstrated irregular concentric lamellar systems.

There has been no examination of human bones from cases of chronic fluoride intoxication. The mottled enamel of human teeth was, however, studied in 1916 by Black [16] and in 1923 by Williams.[17] They had no knowledge of the etiologic factor producing mottled enamel. The former believed that failure of the deposition of cementing substance between the enamel rods produced mottling of the enamel. Williams claimed that mottled enamel was due to imperfectly calcified material in the enamel.

EXPERIMENTAL PROCEDURE

Albino rats [18] weighing from 40 to 60 Gm. were used. Several adult rats weighing 200 Gm. or more were also included in the experiments. The animals were kept in wire cages. The diet that was adequate in calcium consisted of a commercially prepared calf food. The diet that was low in calcium was meat plus cod liver oil and tomato juice. The stock fluoride solution consisted of a liter of distilled water to which 1,000 mg. of sodium fluoride (U. S. P.) was added. The fluoride solution was added to the drinking water. Enough of this solution was given daily so that the rats received doses of 25, 50 or 75 mg. of sodium fluoride per kilogram of body weight. Elementary yellow phosphorus dissolved in olive oil was administered orally by a dropper. The parathyroid extract was injected subcutaneously. The animals were weighed weekly. In series 1, the maximum feeding period was seventeen months. In series 2, 3 and 4, the maximum feeding period varied from two to five months.

Histologic Technic.—The teeth were decalcified in a 2 per cent solution of nitric acid. The incisors and molars were studied in cross and longitudinal sections. The lower incisors were examined especially through the region just anterior to the first molars. Ground disks of some of the incisors were also prepared by Dr. C. F. Bodecker of Columbia University Dental School.

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15. Reed, O. E., and Huffman, C. F.: Michigan Exper. Stat. Quart. Bull. **10**:152, 1928; **13**:137, 1931.

16. Black, G. V.: Dent. Cosmos **58**:129, 1916.

17. Williams, J. L.: J. Dent. Research **5**:117, 1923.

18. The rat has open-rooted incisors, which are necessary for the study of such changes in the teeth. Owen (Odontography, London, H. Baillière, 1840-1845) described the lower incisor of the rat as being the smaller segment of the larger circle and the upper incisor as the larger segment of the smaller circle. The normal size and shape of the rat's incisors are dependent on the proper interaction of the opposing teeth. Any anatomic defect, as loss of an opposing tooth, deviation of the jaw or prognathism of the lower jaw will result in abnormally large incisors. So far as the enamel is concerned, it is found principally on the labial side of the rat's incisor. The enamel is usually yellowish in the young, but becomes orange with age. This is usually more pronounced in the upper incisors than in the lower.

Sections of bone for histologic study were prepared from the lower half of the femur, upper half of the tibia, symphysis pubis, ribs, calvarium and lumbar vertebrae. The bones were fixed in Helly's solution.[18a] Subsequently the bones from one side of the rat's body were decalcified in modified Müller's solution.[19] The bones of the other half were decalcified in a 2 per cent solution of nitric acid. The specimens were embedded in paraffin and stained with hematein and eosin.

Experiments.—The experiments were carried out on rats receiving the following diets:

Series 1: (*a*) an adequate calcium diet (control); (*b*) an adequate calcium diet, plus 25 mg. of sodium fluoride per kilogram of rat daily; (*c*) an adequate calcium diet, plus 25 mg. of sodium fluoride per kilogram of rat daily, plus 0.025 mg. of yellow phosphorus daily; (*d*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily; (*e*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily, plus 0.025 mg. of yellow phosphorus daily.

Series 2: (*a*) an adequate calcium diet (control); (*b*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily; (*c*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily, plus 0.025 mg. of yellow phosphorus daily; (*d*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily, plus the subcutaneous injections of from 5 to 10 units of parathyroid extract daily; (*e*) a diet low in calcium (liberal quantities of meat, cod liver oil and tomato juice), plus 50 mg. of sodium fluoride per kilogram of rat daily; (*f*) a diet low in calcium (liberal quantities of meat, cod liver oil and tomato juice).

Series 3: (*a*) an adequate calcium diet (control); (*b*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily, plus a 2 per cent solution of sodium acid phosphate; (*c*) an adequate calcium diet, plus 50 mg. of sodium fluoride per kilogram of rat daily, plus a 5 per cent solution of sodium acid phosphate.

Series 4: (*a*) an adequate calcium diet (control); (*b*) an adequate calcium diet, plus 75 mg. of sodium fluoride per kilogram of rat daily, plus 0.025 mg. of yellow phosphorus daily.

RESULTS OF THE EXPERIMENTS

Gross Changes in the Teeth.—These depend on the dosage of the toxic agent and the duration of the experiment. When 25 mg. of sodium fluoride per kilogram of rat was added daily to the diet, the rats showed the appearance of striped enamel after three or four months of such feeding. Rats fed for six weeks on an adequate calcium diet plus 50 mg. of sodium fluoride per kilogram of rat daily showed transverse parallel striping of the enamel of the upper and lower incisors. The addition of 0.025 mg. of yellow phosphorus daily, or the subcutaneous

18a. Helly's solution consists of: potassium bichromate, 2.5 Gm.; corrosive mercuric chloride, 5 Gm., and water, 100 cc. Add to 90 cc. of this solution 10 cc. of a 40 per cent solution of neutral formaldehyde, U. S. P., just prior to the fixation of the tissues.

19. This consisted of a 5 per cent aqueous solution of potassium dichromate to which was added 2 cc. of glacial acetic acid per hundred cubic centimeters of modified Müller's solution.

injections of from 5 to 10 units of parathyroid extract daily, did not alter the action of the sodium fluoride on the enamel (fig. 1). The addition of sodium acid phosphate to the fluoride regimen resulted in the appearance of a marble gray enamel after three months. It resembled rather closely that of human mottled teeth (fig. 2*A*).

The stripes in the enamel varied from brown, yellow or orange to a dirty white. The stripe first appeared at the gingival border, and with

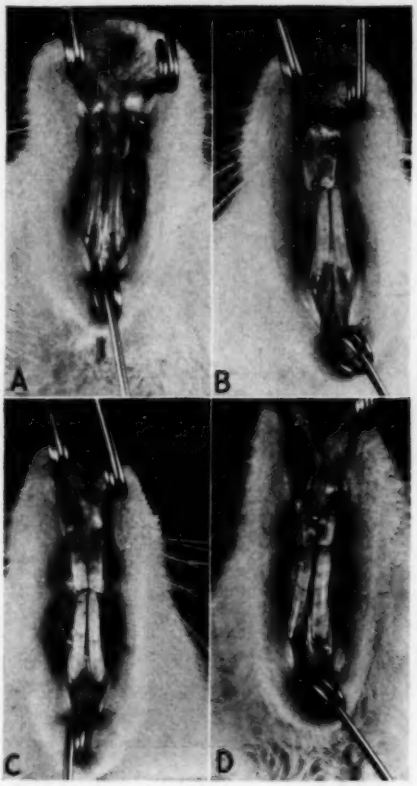

Fig. 1.—*A*, the upper and lower incisors of a control rat fed an adequate calcium diet, showing the normal enamel. *B*, incisors of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) plus 0.025 mg. of elementary yellow phosphorus for seven weeks. *C*, incisors of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for seven weeks. Note the striped enamel of the incisors. *D*, incisors of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) plus daily subcutaneous injections of 5 units of parathyroid extract for seven weeks. Note the striped enamel of the incisors.

a rapidity depending on the rate of growth, reached the occlusal end of the incisor. A zebra-like striping of the enamel was often evident

after the feeding of sodium fluoride in the amount of 50 mg. per kilogram of body weight for from six to eight weeks.

When sodium fluoride was given in amounts of 50 mg. per kilogram of rat daily for three months, backward curving of the upper incisors was noted. From four to six months or more of similar dieting caused the upper incisors to curve almost to a complete circle (fig. 2*C* and *D*). When such abnormal curving set in, the enamel of the incisors might

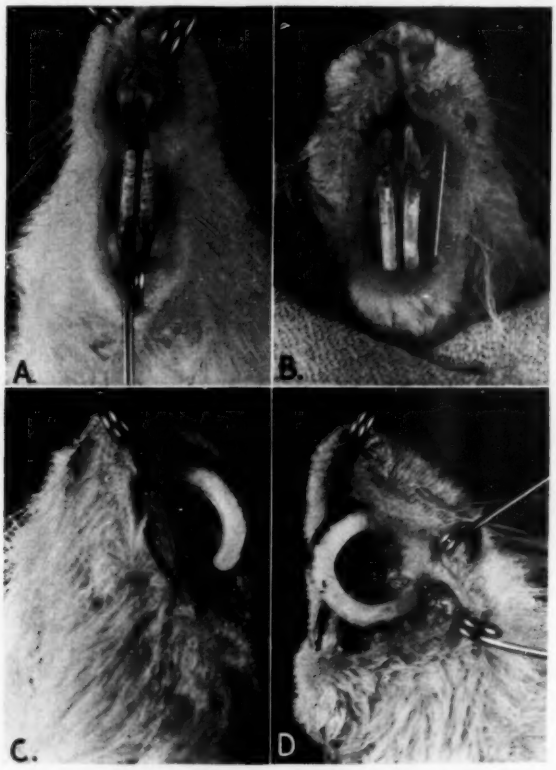

Fig. 2.—*A*, upper and lower incisors of a rat receiving an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) plus a 5 per cent solution of sodium acid phosphate for three months. Note the triangles of pigmented enamel in the upper incisors and the granular, grayish enamel in the lower ones. *B*, incisors of a rat receiving an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for eleven months. Note the loss of the upper incisors, the compensatory elongation of the lower incisors and the erosion and irregularity of the enamel of the lower incisors. *C*, incisors of a rat receiving an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for seven months. Note the loss of pigment and erosion of the enamel and the backward curving of the upper incisors. *D*, incisors of a rat receiving an adequate calcium diet plus sodium fluoride (25 mg. per kilogram of rat daily) for fifteen months. Note the marked corrugation of the enamel as well as the marked curving of the upper incisor.

lose its striped bands either partially or completely and present a white or dirty white appearance. On the other hand the upper incisors, instead of becoming lengthened, might become shortened, and because of this there was an increase in size of the lower incisors (fig. 2*B*). This disproportion was the result of imperfect occlusion between the upper and lower incisors.

After three or four months while the incisors were curving, the surface of the enamel tended to become corrugated. In several of the rats, the attrition from the lower incisors produced visible depressions on the medial surfaces of the upper incisors. In others fixed deformities in abduction of the upper incisors were seen. (The rat can voluntarily abduct the two halves of the lower jaw, but not those of the upper.) The upper teeth might curve so that their biting edges were located outside of the mouth cavity. The upper or lower incisors were liable to chip or break quite easily. In many the pulps, especially those of the lower incisors, were completely exposed. The occlusal surfaces were completely deranged; the biting edges were irregular, chipped and eroded. Some portions of the enamel presented a scaly appearance. Since enamel is not present on the lingual surface, nothing unusual was seen there. Examination of the incisors and molar teeth with a high magnifying lens failed to reveal the presence of gross dental caries. (McKay has shown that caries is not more common in children having mottled enamel than among those having nonmottled enamel.) The molars showed none of the changes described for the incisors.

Appearance of the Incisor Teeth in Roentgenograms.—Roentgenographic examination of the upper and lower incisors clearly revealed the deformities seen grossly. In the upper incisors excessive dentin encroached on the pulp cavity. This gave a more opaque shadow in the roentgenogram as compared with that of the dentin of normal incisors (fig. 3). On the other hand, the dentin of the upper incisors of animals on a low calcium diet, but protected with vitamins, was much thinner than normal. The roentgenograms of the incisors of fluoride-fed animals showed erosion of the enamel, irregular biting edges and deep alternating elevations and depressions.

Histologic Changes in the Teeth.—Examination of the incisors revealed many of the already recognized changes. There was ameloblastic inactivity as evidenced by flattening of the ameloblasts. A diminution of pigment was noted in the ameloblastic layer. The blood supply in the papillary area was also reduced. Herniation of the ameloblasts extended into the enamel. There were also inclusions of enamel in the ameloblastic layer (fig. 4*A*). Some of the preparations of the teeth showed accentuations of the linear markings of the enamel with the occasional presence of calcospherites. Eroded and imperfect enamel was a prominent change (figs. 4*B*, 4*C*, 5*A* and 5*B*). The dentin, instead of being homogeneous or

occasionally imperfectly calcified as in a normal rat's incisors, appeared stratified by parallel lines in many histologic preparations (fig. 5*C*). In some sections, cystlike areas were noted in the dentin due to acalcification. Some sections bore evidence of the presence of the pyknotic nuclei of odontoblasts in the depths of the dentin. Many of the stripes in the dentin varied in thickness. The boundary between the predentin and dentin was wavy in many of the sections. The width of the zone of

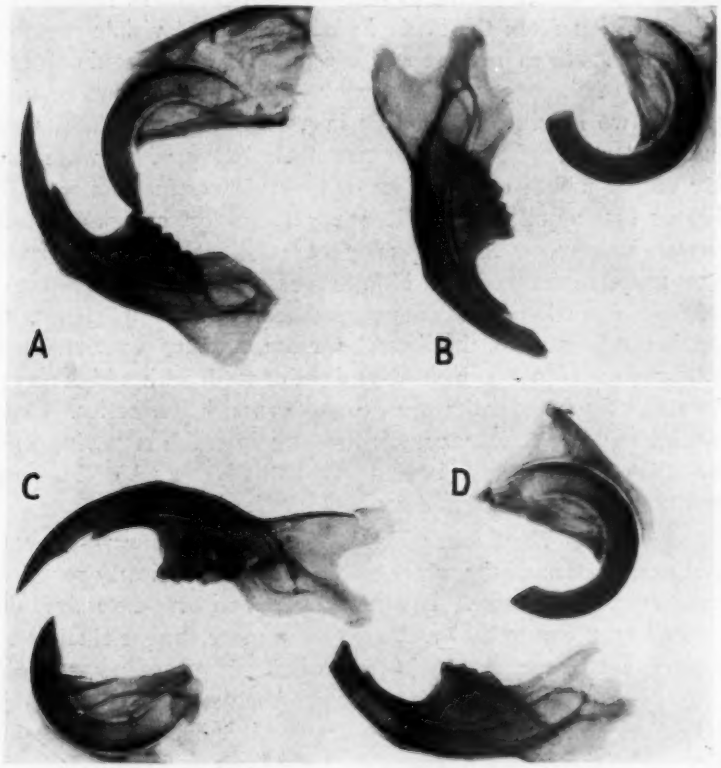

Fig. 3.—*A*, upper and lower incisors of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for six weeks. Note the slight increase in the backward curvature of the upper incisor. *B*, incisors of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for fourteen weeks. Note the backward curvature of the upper incisors, the increase in the density of the shadow cast by the dentin and the irregular occlusal surfaces of the incisors. *C*, incisors of a rat fed an adequate calcium diet. Note the normal appearance. *D*, incisors of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) plus daily subcutaneous injections of 5 units of parathyroid extract for fourteen weeks. The changes in the teeth are similar to those in figure 3 *B*.

predentin was slightly greater than normal. Slight flattening of the odontoblasts and protrusions of the pulp into the dentin were noted. The

molar teeth showed nothing striking except dentinal protrusions into the pulp. The injections of parathyroid extract or the feeding of yellow phosphorus plus sodium fluoride in the doses noted in no way altered the histologic picture produced by sodium fluoride alone. Similarly the ingestion of sodium acid phosphate plus sodium fluoride produced no

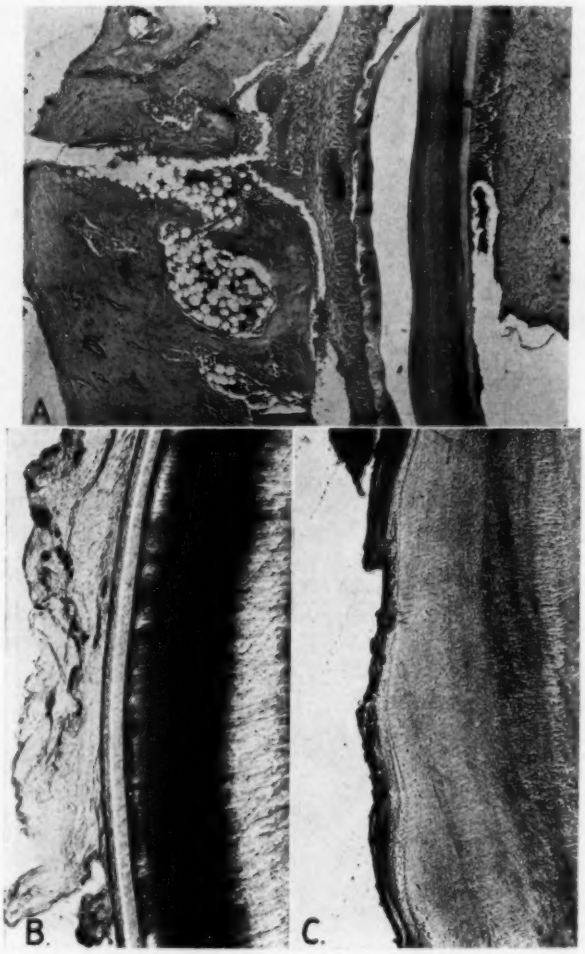

Fig. 4.—*A*, low power photomicrograph of the incisor of a rat fed an adequate calcium diet plus sodium fluoride (25 mg. per kilogram of rat daily) for four months. Note the inclusion of enamel in the ameloblastic layer, the numerous ameloblastic herniations into the enamel and the stratification of the dentin (× 60). *B*, low power photomicrograph of an upper incisor (ground disk) of a control rat (× 30). *C*, low power photomicrograph of an upper incisor (ground disk) of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for four months. Note the eroded and abnormal enamel and the stratification of the dentin (× 30).

striking variations. Schour and Ham,[20] however, recently showed changes in the zones of dentin and predentin from the injections of larger doses of parathyroid extract alone.

The chief results, therefore, of the feeding of sodium fluoride, so far as the incisors are concerned, are impairment of the production of

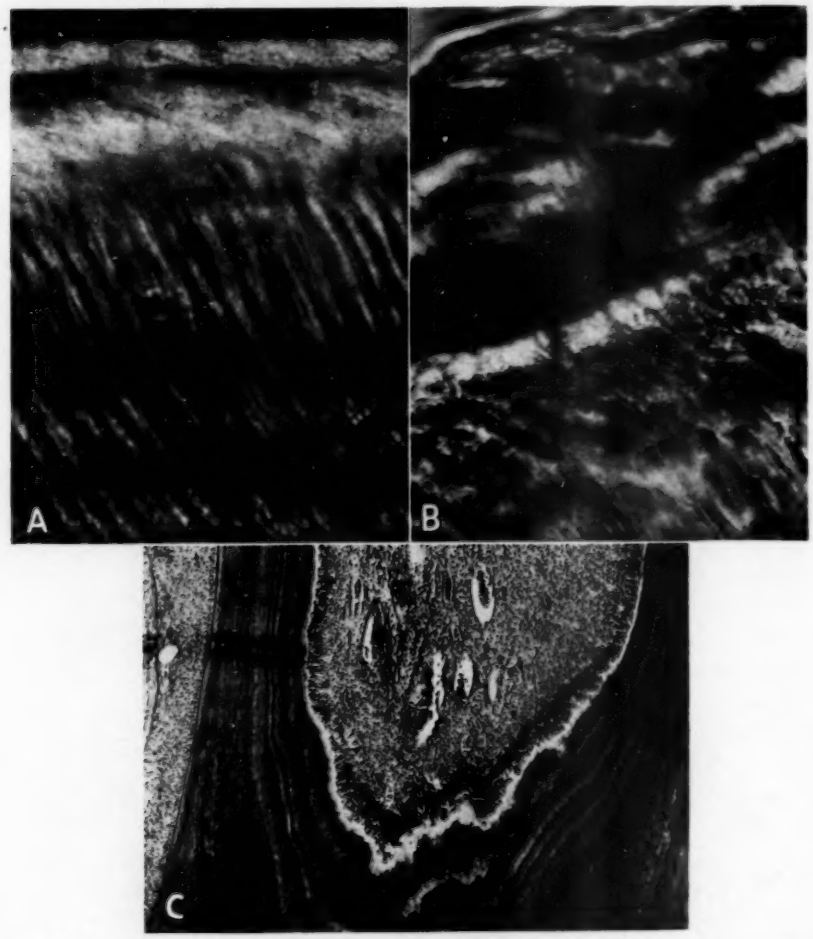

Fig. 5.—*A*, high power photomicrograph of normal enamel in figure 4 *B*. Note the enamel prisms and the external membrane (reduced from × 2,250). *B*, high power photomicrograph of the abnormal enamel in figure 4 *C*. Note the amorphous character of the enamel (reduced from × 2,250.). *C*, photomicrograph of the upper incisor of a rat fed an adequate calcium diet plus sodium fluoride (25 mg. per kilogram of rat daily) for three weeks. Note the stratification of the recently formed dentin (× 40).

20. Schour, I., and Ham, A. W.: J. Dent. Research **13**:194, 1933; Arch. Path. **17**:22, 1934.

enamel tissue and imperfect calcification of both the dentin and the enamel.

Gross and Microscopic Changes in the Bones of Fluoride-Fed Rats.—The bones of rats fed varied amounts of sodium fluoride revealed no deformities. The bones of the animals fed 50 mg. of sodium fluoride for five or more months were dull, white and quite brittle. The sections revealed that there may have been some diminished formation of bone at the epiphyseal plates, but that there were no evidences of osteoclastic activity, osteoporosis or changes peculiar to any of the known vitamin or metabolic deficiencies.

The bones, partially decalcified with Müller's fluid plus acetic acid, revealed changes not observed in those decalcified with nitric acid. The partially decalcified bones stained unusually dark with hematein and eosin in many instances (fig. 6*A*). The fibrils in the bone were often easily perceived. The changes in the various series are summarized as follows:

Series 1: Histologic sections of the bones of rats fed sodium fluoride (50 mg. per kilogram of rat daily) for a year or more showed irregularity of the fibrils of the matrix. Numerous coarse and fine dark-staining granules were noted among the fibrils of the bone and also in the lighter staining bone. Some of the granules were observed in the atypically staining matrix about pyknotic bone cells; others were noted in the borders of haversian canals (fig. 6*B*). It appeared that the granules of the matrix of the bone actually replaced portions of the fibrils, probably increasing the matrix content and diminishing the fibrillar content.

Although the granulation of the matrix generally appeared after a year or more of ingestion of sodium fluoride (50 mg. per kilogram of rat daily), localized areas of granular matrix could be noted after shorter periods of experimentation. A rat, weighing 280 Gm. at the onset of the experiment, showed a granular appearing layer of circumferential lamellar bone after four months of experimental feeding. The tibia of this rat presented a granular appearance in a portion of one of the large trabeculae.

Some of the cortices of several rats (fed 50 mg. of sodium fluoride per kilogram of rat daily) for a year or more showed a lattice-like and stratified arrangement, that is, areas of dark-staining bone alternating with irregularly shaped, light-staining bone. Dark-staining granules were present in the lighter zones and also among the individual dark fibrils. In an animal fed for fifteen months with sodium fluoride (50 mg. per kilogram of rat daily) large irregular granules were found in the interpubic ligament similar to those present in the bone (fig. 6*C*). In some of the bones of rats fed sodium fluoride (50 mg.

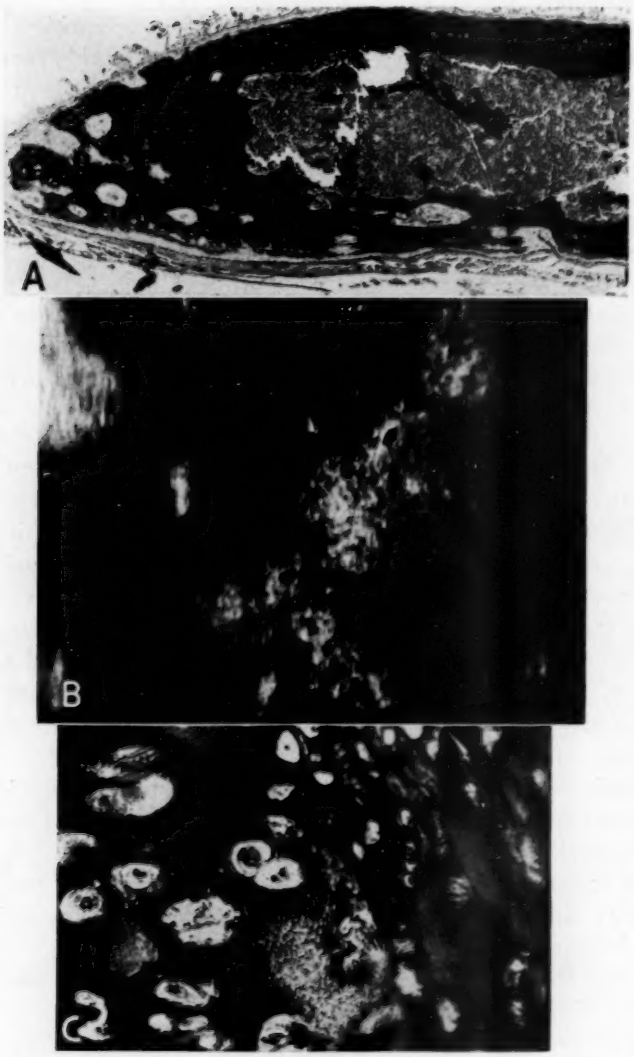

Fig. 6.—*A*, photomicrograph of the cortex of a rib from a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for fifteen months. Note the dark staining of the bone and the irregular granular appearance near the periosteum (reduced from × 35). *B*, high power photomicrograph of an area from figure 6 *A*. Note the irregular coarse and fine dark staining granules about the pyknotic bone cells among the dark fibrils (reduced from × 750). *C*, high power photomicrograph of the interpubic ligament of a rat fed an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for fifteen months. Note the deposition of localized fine granules in the hyaline cartilage (reduced from × 900).

per kilogram of rat daily) for a year or more, the marrow showed hemorrhages, an increase in polymorphonuclear cells and occasional cysts due to degeneration.

Series 2: Rats kept on an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for from three to five months showed

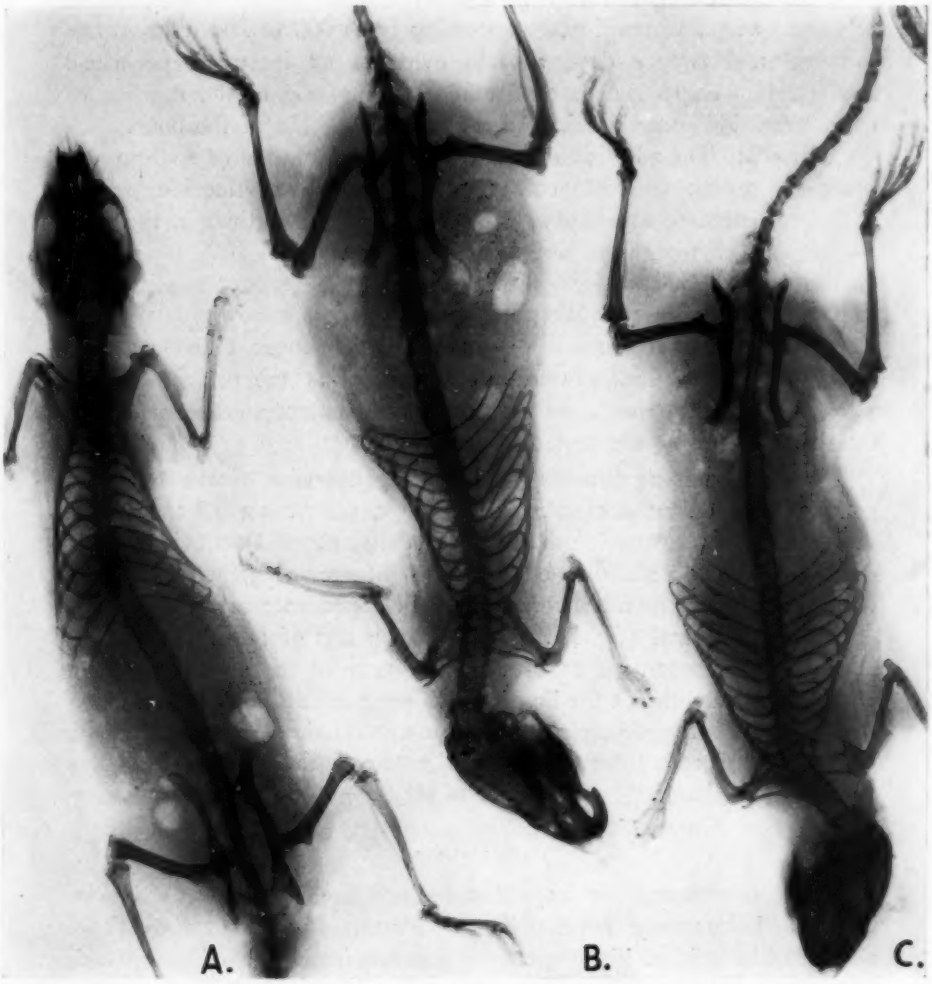

Fig. 7.—*A*, roentgenogram of a control rat. *B*, roentgenogram of a rat receiving an adequate calcium diet plus sodium fluoride (50 mg. per kilogram of rat daily) for four months. Note the slight increase in density of the bones as compared to those in figure 7 *A*. *C*, roentgenogram of a rat receiving a diet similar to the rat in figure 7 *B*, plus daily subcutaneous injections of 5 units of parathyroid extract for four months. Note the slight increase in the density of the bones as compared to those in figure 7 *A*.

no unusual changes in the bones. Rats on a diet low in calcium plus sodium fluoride died from one to two months after the onset of the experiment. The skeletal system of rats on this diet showed a marked generalized osteoporosis. It is of interest that in one of the animals irregular, dark-staining granules were noted in an atrophic trabecula of the tibia. Animals receiving sodium fluoride with the addition of injections of parathyroid extract totaling from 600 to 700 units in one hundred and twenty days showed evidence of increased periosteal activity, Howship's lacunae and a marked increase in the number of osteoclasts. No granules were seen among the fibrils of the bone.

Series 3: The addition of a 2 or 5 per cent solution of sodium acid phosphate to an adequate calcium diet plus sodium fluoride yielded slight evidences of atrophy of the trabeculae and cortices in the ribs. No unusual changes were noted in the other bones.

Series 4: The examination of the bones of the rat receiving 75 mg. of sodium fluoride per kilogram of rat daily for seventy-five days showed an unusual amount of osteoid tissue about each haversian canal. Numerous dark granules were present at the osteoid borders as well as in the matrix near the enlarged lacunae of the cells. No osteoclastic activity was noted.

Roentgenographic Studies.—The roentgenograms of the bones of animals kept on an adequate calcium diet, plus from 25 to 50 mg. of sodium fluoride per kilogram of rat daily, showed no evidences of osteoporosis. The shadows of the bones of animals kept on the diet for four or more months were normal in appearance or slightly more opaque than normal (fig. 7). Animals on a diet of 50 mg. of sodium fluoride per kilogram of rat daily for a year or more showed roentgenographic shadows of the bones which were equal to or slightly denser than those of the controls. (Experimental animals dying of some intercurrent disease sometimes showed osteoporosis.) The addition of sodium acid phosphate resulted in a very slight thinning of some of the bones.

COMMENT

These experiments indicate that sodium fluoride produces changes in teeth before any appear in the bones. In the osseous tissue abnormalities evident histologically occur in animals fed sodium fluoride for a year or more. Whether the alterations in the bone are due to the deposition of fluoride or to other substances cannot be definitely stated. The changes in the matrix of the bone occur without the intervention of osteoclasts. It seems that the modifications in the matrix of the bone do not develop in a systematic fashion. They result either from changes in the matrix of the original bone or from the deposition of new bone with an abnormal matrix. Similarly there are no definite sites of predilection for changes in the matrix.

The roentgenographic examination of the bones of the experimental animals, except those on a diet low in calcium or those receiving sodium acid phosphate, showed no osteoporosis. In animals fed sodium fluoride (50 mg. per kilogram of rat daily) for periods of twelve or more months, increased density of the bones was noted on comparison with the controls. This was less marked in animals fed this diet for periods of less than twelve months. This is of interest, for recently an important contribution in regard to fluoride intoxication was made by Moeller and Gudjonsson.[2] They found by roentgenographic studies of the skeletal system that thirty out of seventy-eight workers exposed to the effects of cryolite, a fluoride compound, showed varying degrees of osteosclerosis (with secondary anemia). It would be interesting to ascertain any possible relationship between fluoride intoxication and other osteosclerotic diseases, as Paget's disease, idiopathic osteosclerosis or marble bone disease (Albers-Schönberg). It may be pointed out that feeding of sodium fluoride in no way leads to the production of the type of bone ordinarily seen in Paget's disease.

The alterations in the teeth of fluoride-fed animals have been assigned to endocrine factors. Bergara,[5] Chaneles [6] and Pavlovic and Tihomirov [21] expressed the belief that sodium fluoride acts directly on the parathyroid glands and thus secondarily produces changes in teeth. In our experiment, parathyroid extract, given up to a total of 700 units over a period of two or three months, neither retarded nor prevented the appearance of striped enamel. Hauck and his co-workers [22] recently called attention to the fact that demonstrable histologic changes were not present in the parathyroid glands of fluoride-fed animals.

CONCLUSIONS

Sodium fluoride in doses of 50 mg. per kilogram of rat daily for six weeks produces changes in the enamel of the incisors.

Sodium fluoride in doses of 50 mg. per kilogram of rat daily for a period of a year or more causes changes in the matrix of the bones which is evident histologically.

The changes in the teeth and bones are due principally to a chemical disturbance which is unrelated to the parathyroid glands.

The appearance of osteosclerosis, in both clinical and experimental chronic fluoride poisoning, may throw some light on the etiology of idiopathic osteosclerotic diseases.

Certain of the cases of Paget's disease or marble bone disease should be examined in this light.

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21. Pavlovic, R. A., and Tihomirov, M. T.: Compt. rend. Soc. de biol. **110:** 497, 1932.

22. Hauck, H. M.; Steenbock, H., and Parsons, H. T.: Am. J. Physiol. **103:** 480, 1933. Hauck, H. M.; Steenbock, H.; Lowe, J. T., and Halpin, J. G.: Poultry Sc. **12:**242, 1933.

EFFECT OF RESECTION OF LARGE FRACTIONS OF RENAL SUBSTANCE

AN EXPERIMENTAL STUDY

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The work of several investigators, notably de Paoli,[1] Mauchle,[2] Fiori[3] and Tuffier,[4] has established the fact that in animals life can be sustained with one third of the normal amount of renal substance. Bradford[5] and Bainbridge and Beddard[6] independently showed that if the amount of renal tissue was reduced to one fourth death occurred in from one to six weeks. Pearce,[7] however, found that if compensatory hypertrophy had taken place three fourths of the substance of the kidneys of dogs could be removed without loss of life and the normal value for nonprotein nitrogen of the blood was maintained. Mann and Bollman[8] have noted that in puppies compensatory hypertrophy after unilateral nephrectomy and resection of the upper pole of the opposite kidney was distinguished by a marked tendency toward restoration of the normal contour of the organ.

These observations prompted the present study, which represents the preliminary research in a series of investigations on the general problem of compensatory renal hypertrophy, the cause and mechanism of which are not fully understood. This subject is of considerable practical importance because the success of many of the operations on the human kidney depends on the capacity of the organism to adapt itself to losses

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Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Ph.D. in urology.

1. de Paoli, E.: Della resezione del rene: Studio sperimentale, Perugia, Boncompagni, 1891.
2. Mauchle, A.: Beitrag zur Kenntnis der kompensatorischen Hypertrophie der Niere, Zurich, Art. Institut Orel Füssli, 1894.
3. Fiori, Paolo: Policlinico (sez. chir.) **8**:349 and 428, 1901.
4. Tuffier, M.: Bull. Soc. anat. de Paris **63**:447, 1888.
5. Bradford, J. Rose: J. Physiol. **23**:415, 1899.
6. Bainbridge, F. A., and Beddard, A. P.: J. Physiol. **35**:xxi, 1906-1907.
7. Pearce, R. M.: J. Exper. Med. **10**:632, 1908.
8. Mann, F. C., and Bollman, J. L.: Unpublished data.

of large fractions of renal substance, a capacity which to a considerable extent can be attributed to the phenomenon of compensatory hypertrophy.

In this and in subsequent experiments, litter mate animals were used so that variable factors resulting from differences in age would be controlled and the animals, because they were of the same breed and family, would possibly be subject to less variation than animals in which the hereditary factors were not the same.

For the first research, herein reported, litter mate puppies, aged from 5 to 6 months, comprising one litter of four animals and two litters of two animals each, were used. The plan consisted in excising the right

TABLE 1.—*General Data on Animals of Litter 1 (Four Mongrel Terrier Puppies)*

Animal and Sex	Operation		Necropsy		Operation and Kidney Observed at Necropsy	Weight of Kidney, Gm.	External Dimensions of Kidney, Cm.			Thickness, Cm.	
	Age, Weeks	Body Weight, Kg.	Age, Weeks	Body Weight, Kg.			Length	Width	Thickness	Cortex	Medulla
1 M	30	5.8	..	...	Nephrectomy (right side)	18.6	4.95	2.16	2.21	0.54	1.15
			70	8.0	Left kidney (necropsy)	39.3	5.90	2.72	3.08	0.83	1.40
2 F	30	5.6	..	...	Nephrectomy (right side)	16.6	4.64	2.27	2.17	0.52	1.23
	30	5.6	..	...	Resection of upper pole of left kidney	4.3	2.34 2.00	2.20	2.07	0.55	1.00
			70	5.8	Left kidney (necropsy)	29.5	4.73	2.85	2.90	0.64 0.87	1.40
3 F	30	7.1	..	...	Nephrectomy (right side)	20.9	5.15	2.28	2.41	0.66	1.10
	30	7.1	..	...	Resection of upper pole of left kidney	7.9	2.68 3.10	2.90	2.40	0.51	0.84
			70	7.8	Left kidney (necropsy)	43.9	5.87	3.44	3.55	0.95 1.18	1.30
4 F	30	5.4	..	...	Nephrectomy (right side)	16.8	4.70	2.00	2.09	0.57	1.05
	30	5.4	..	...	Resection of upper pole of left kidney	6.8	2.35 2.73	2.50	2.30	0.61	1.05
	55	5.7	..	...	Resection of lower pole of left kidney	8.4	1.82	3.45	2.53	0.66	0.73
			70	5.7	Left kidney (necropsy)	21.3	3.63	3.20	3.38	0.86 0.103	1.10

kidney in all the animals and in carrying out also a partial resection of the left kidney in all the animals except one, the control, of each litter. All the operative procedures were performed under ether anesthesia, and the routine surgical technic was employed. After several months the animals were killed, and the degree and character of the hypertrophic process in each animal were compared with those in its mate or mates. Quantitative observations (tables 1 to 6) were recorded, including measurements of the diameters of renal corpuscles and convoluted tubules. For the latter purpose a filar screw micrometer was used. Twenty corpuscles and twenty convoluted tubules were taken at random for measurement, in representative sections of renal cortex (table 4).

TABLE 2.—*General Data on Animals of Litter 2 (Two Mongrel Shepherd Puppies) and on Litter 3 (Two Mongrel Terrier Puppies)*

Litter	Animal and Sex	Operation: Age, Weeks	Operation: Body Weight, Kg.	Necropsy: Age, Weeks	Necropsy: Body Weight, Kg.	Operation and Kidney Observed at Necropsy	Weight of Kidney Gm.	External Dimensions of Kidney, Cm.: Length	Width	Thickness	Thickness, Cm.: Cortex	Medulla
2	5 F	24	9.2	..	....	Nephrectomy (right side)	19.2	5.42	2.39	2.16	0.54	1.43
				60	12.4	Left kidney (necropsy)	46.2	6.60	3.10	3.10	0.68	1.43
2	6 F	24	10.2	..	....	Nephrectomy (right side)	25.6	5.50	2.44	2.44	0.52	1.23
		24	10.2	..	....	Resection of upper pole of left kidney	11.7	3.57 2.35	2.64	2.66	0.55	1.27
				60	12.3	Left kidney (necropsy)	30.9	4.85	3.40	2.57	0.73 0.93	1.73
3	7 M	26	7.6	..	....	Nephrectomy (right side)	22.1	5.10	2.48	2.38	0.56	1.22
				53	10.8	Left kidney (necropsy)	43.7	6.10	3.13	2.80	0.70	1.14
3	8 M	26	8.8	..	....	Nephrectomy (right side)	26.3	5.40	2.50	2.50	0.61	1.45
		26	8.8	..	....	Resection of upper pole of left kidney	9.6	2.30 3.56	3.10	2.15	0.58	1.27
				53	14.6	Left kidney (necropsy)	51.8	5.45	5.09	2.98	0.76 1.18	1.23

TABLE 3.—*Comparison of Body Weights and Weights of Hypertrophied Kidneys Showing Absolute and Relative Changes*

Litter	Animal	Sex	Increase in Body Weight: Kg.	Increase in Body Weight: Percentage	Combined Weight of Resected Renal Tissue: Gm.	Combined Weight of Resected Renal Tissue: Percentage	Increase in Renal Weight, Hypertrophy: Gm.	Increase in Renal Weight, Hypertrophy: Percentage	Relation of Renal Weight to Body Weight: Index Number*
1	1	M	2.2	37.9	18.6	50.0	20.7	111.33	4.92
	2	F	0.2	3.6	21.0	63.1	17.2	103.23	5.10
	3	F	0.6	8.45	28.8	68.9	30.9	147.74	5.63
	4	F	0.3	5.55	32.1	95.4†	19.7	117.32	3.57
2	5	F	3.2	34.8	19.2	50.0	27.0	140.62	3.73
	6	F	2.1	20.6	37.3	72.8	16.9	66.33	2.51
3	7	M	3.2	42.1	22.1	50.0	21.6	97.52	4.05
	8	M	5.8	65.9	36.0	68.4	35.1	133.59	3.55

* The index number was obtained by dividing the renal weight in grams by the body weight in kilograms. The quotient thus obtained indicates the number (index) of grams of renal tissue per kilogram of body weight.

† In this animal 70.2 per cent of the renal substance was resected at the first operation. After hypertrophy had occurred (twenty-five weeks) another segment was removed. Hence, the actual percentage of original renal substance resected was less than 95.4 and more than 70.2 per cent.

TABLE 4.—*Diameters of Renal Corpuscles and Convoluted Tubules of Normal (Extirpated Right) and Hypertrophied (Left) Kidneys*

Litter	Animal	Sex	Age, Weeks	Kidney	Diameters, Microns: Renal Corpuscles* Mean Value for 20 Corpuscles	Renal Corpuscles* Range of Values	Convoluted Tubules* Mean Value for 20 Tubules	Convoluted Tubules* Range of Values
1	1	M	30	Right	113.0	91-129	43.6	37-51
		M	70	Left	134.9	125-142	46.0	40-52
1	2	F	30	Right	109.5	93-124	39.8	33-45
		F	30	Upper pole of left kidney	105.2	92-120	39.4	35-44
		F	70	Left	139.4	129-148	45.6	39-51
1	3	F	30	Right	113.3	104-127	39.6	35-45
		F	30	Upper pole of left kidney	114.3	98-132	43.2	37-54
		F	70	Left	154.2	142-172	54.3	49-63
1	4	F	30	Right	108.2	86-121	41.2	36-47
		F	30	Upper pole of left kidney	104.4	85-125	39.0	33-45
		F	55	Lower pole of left kidney	145.4	130-174	55.2	48-63
		F	70	Left	167.2	141-192	58.7	48-71
2	5	F	24	Right	106.2	89-145	38.0	32-46
		F	60	Left	132.0	121-143	41.8	38-46
2	6	F	24	Right	111.9	90-132	38.3	32-46
		F	24	Upper pole of left kidney	116.4	90-135	39.4	34-49
		F	60	Left	170.4	140-210	57.9	47-66
3	7	M	26	Right	94.0	83-110	39.4	30-47
		M	53	Left	139.8	108-173	45.6	38-55
3	8	M	26	Right	104.5	87-124	35.5	30-43
		M	26	Upper pole of left kidney	104.2	90-121	37.0	31-44
		M	53	Left	156.9	134-178	54.4	47-74

* The diameters of twenty corpuscles and tubules were measured, but only their mean and range values are recorded.

TABLE 5.—*Absolute and Relative Differences Between Diameters of Renal Corpuscles and Convoluted Tubules of Normal and Those of Hypertrophied Kidneys*

Litter	Animal	Sex	Time Between Operation and Necropsy, Weeks	Increase in Values for Microscopic Measurements of Hypertrophied Left Kidney over Normal Right Kidney: Renal Corpuscles Microns	Renal Corpuscles Percentage	Convoluted Tubules Microns	Convoluted Tubules Percentage
1	1	M	40	21.9	19.4	2.4	5.5
1	2	F	40	29.9	27.3	5.8	14.6
1	3	F	40	40.9	36.1	14.7	37.1
1	4	F	25*	37.2	34.4	14.0	33.9
		F	40	59.0	54.5	17.5	41.9
2	5	F	36	25.8	24.3	3.8	10.0
2	6	F	36	58.5	52.3	19.6	51.2
3	7	M	27	45.8	48.7	6.2	15.7
3	8	M	27	52.4	50.3	18.9	53.2

* Resection of lower pole.

The partial resection was accomplished by severing the upper pole and in one instance, at a second operation, also the lower pole (fig. 1 *D*) with a guillotine sweep of the knife, while the flow of blood was controlled by means of a serrefine on the pedicle. A running suture of fine silk thread was then passed through and through the capsule and cortex on the outside and through the pelvis and medulla within, thus controlling hemorrhage. In no case did postoperative bleeding occur.

OBSERVATIONS AND COMMENT

Litter 1 consisted of four mongrel terrier puppies, one male and three females, aged 30 weeks when the experiment was begun and 70

TABLE 6.—*Comparison of Weight of Resected Renal Tissue with Percentage Increase in Diameters of Renal Corpuscles and Convoluted Tubules of Remaining Segment of Hypertrophied Kidney* *

Litter	Animal	Sex	Time Between Operation and Necropsy, Weeks	Combined Weight of Resected Renal Tissue		Percentage of Increases in Values for Microscopic Measurements of Hypertrophied (left) Kidney Over Normal (right) Kidney	
				Gm.	Percentage of Total Weight†	Renal Corpuscles	Convoluted Tubules
1	1	M	40	18.6	50.0	19.4	5.5
1	2	F	40	21.0	63.1	27.3	14.6
1	3	F	40	28.8	68.9	36.1	37.1
1	4	F	25 (Removal of upper pole of left kidney)	23.6	70.2	34.4	33.9
	4	F	40 (Removal of lower pole of left kidney)	32.1	95.4	54.5	41.9
2	5	F	36	19.2	50.0	24.3	10.0
2	6	F	36	37.3	72.8	52.3	51.2
3	7	M	27	26.3	50.0	48.7	15.7
3	8	M	27	36.0	68.4	50.3	58.2

* The normal right (extirpated) kidney was used as the standard of comparison.
† The approximate total weight of renal tissue was calculated by doubling the weight of the normal right (extirpated) kidney.

weeks when it was terminated. Animal 1 served as a control; a simple excision of the right kidney only was performed on this animal. In the remaining animals, in addition to the nephrectomy, the upper pole of the left kidney was resected at the same operation. In animal 4 the lower pole also was resected at a second operation, twenty-five weeks after the initial operation, when the animal was aged 55 weeks.

At intervals throughout the experiment estimations of the concentration of the blood urea were made. Although a considerable elevation in values occurred following the resection, after intervals of from two to three weeks all the values were within normal limits, including the values for the animal from which the largest fraction of renal substance (more than three-fourths) had been removed in stages.

Analyses of the urine of all the animals made at the outset and at the end of the experiments gave no evidence of abnormalities.

Readings of the blood pressure, taken by the indirect method, varied widely but were within normal limits. Significant elevations did not

occur following resection of large fractions of renal substance. Direct readings of the femoral arterial blood pressure, taken by the cannula-mercury manometer method under local anesthesia just before necropsy, were normal and of the same magnitude for each of the four animals of litter 1.

Progressively larger amounts of renal substance were resected from successive animals of this litter as follows: animal 1, 50 per cent; animal 2, 63.1 per cent; animal 3, 68.9 per cent, and animal 4, 95.4 per cent. Each percentage was computed from the weight of the resected tissue and from the estimated total weight of the renal substance at the outset of the experiment. The approximate total initial weight was calculated by doubling the weight of the right (excised) kidney. It should be noted that the computed weight of the total renal substance

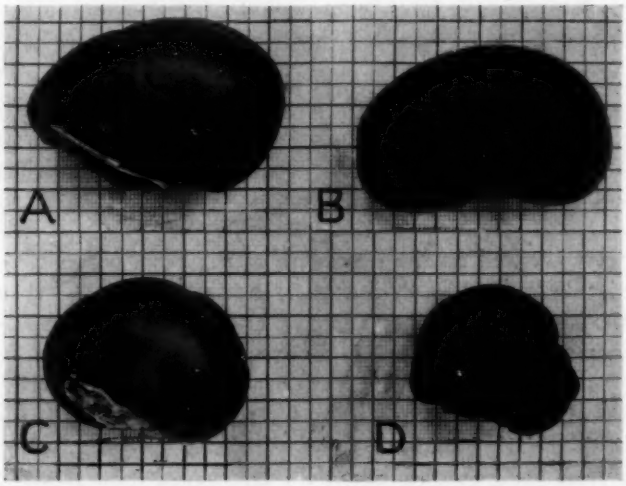

Fig. 1.—Hypertrophied kidneys of animals of litter 1, photographed on centimeter coordinate paper. The abnormality of the contour of the kidneys which had been subjected to partial resection is evident. *A*, kidney from animal 3, renal weight 43.93 Gm.; *B*, kidney from animal 1, renal weight 39.35 Gm.; *C*, kidney from animal 2, renal weight 29.56 Gm.; *D*, kidney from animal 4, renal weight 21.33 Gm.

may show an error, being slightly larger than the actual weight, because in dogs, as in most mammals, the right kidney is usually approximately 5 per cent larger than the left. The quoted values for animals 1, 2 and 3, therefore, are probably slightly smaller than they would be if the actual weights of the left kidneys were known. Two operations were performed on animal 4; at the first, 70.2 per cent of the renal substance was removed; at the second, after some hypertrophy had occurred another segment was removed, bringing the value of the substance removed to 95.4 per cent. Since the second resection included hyper-

trophied renal tissue, the actual value must lie somewhere between 70.2 and 95.4 per cent. Probably, therefore, not less than three fourths of the renal substance present at the outset of the experiment was ultimately removed.

The greatest relative increase in weight (normal growth plus hypertrophy) of the remaining segment of kidney, namely, 147.74 per cent, occurred in animal 3. An amount of renal substance equivalent to 68.9 per cent of the original weight of both kidneys taken together was resected. Notwithstanding this fact, the hypertrophied remaining segment provided more renal tissue per kilogram of body weight (index number, 5.63) than was provided by the corresponding segment in animals 1 and 2, from which lesser relative amounts of kidney were resected. However, when a larger relative amount, somewhat more than three fourths, was resected from animal 4, the increase in weight of the kidney was limited to 117.32 per cent, and the index number was 3.57. This finding clearly suggests that there is a limit to the capacity of the remaining segment of kidney to react by hypertrophy, although the possibility of injury to the blood vessels in the course of the resection cannot be eliminated as a factor in limiting hypertrophy. It should be noted that although the hypertrophied segment of kidney which remained was small it was able to maintain a normal concentration of urea in the blood.

Data were secured on the diameters of the renal corpuscles and the convoluted tubules (tables 4, 5 and 6) as well as on the relationship between the amount of kidney resected and the percentage of increase of the diameters in the remaining (hypertrophied) segment over the diameters as measured in renal tissue removed at the beginning of the experiment (table 6). The results for litter 1 indicate that with an increase in the relative amount of tissue resected an increase in the size of the corpuscles and tubules occurs. Thus, comparing animals 1 and 4, in the former 50 per cent of the renal substance was resected and the increase in the diameters of the corpuscles and of the tubules was 19.4 per cent and 5.5 per cent, respectively, whereas in the latter (animal 4) at least 75 per cent of the renal substance was resected and the diameters of the corpuscles and of the tubules were increased by 54.5 per cent and 41.9 per cent, respectively. The same general relationship is true for litters 2 and 3. In animal 6, 72.8 per cent of the renal substance was removed at one operation, and the animal survived. The response by hypertrophy was limited to 66.33 per cent, again suggesting, as for litter 1, that an excessive resection may inhibit the hypertrophic response. Animal 8 (litter 3) reacted by marked hypertrophy, 133.59 per cent, after 68.4 per cent of renal substance had been resected, but in this animal considerable bodily growth (65.9 per cent) occurred, a feature which was less marked in the animals of litter 2 (34.8 per cent and

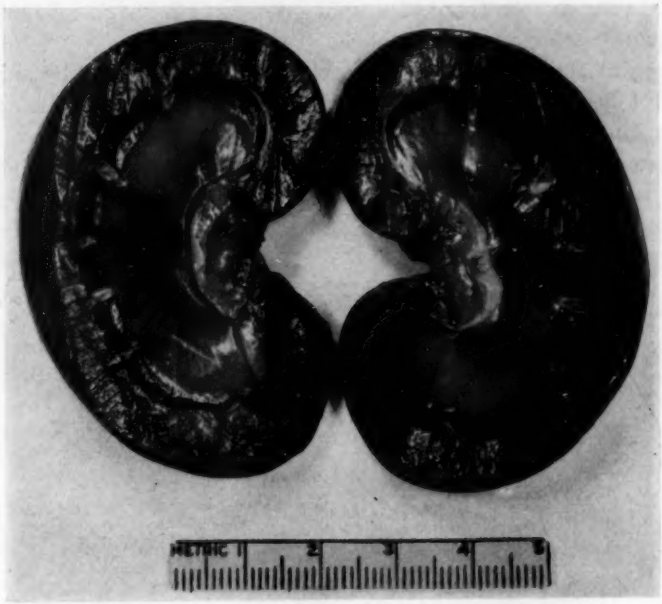

Fig. 2 (animal 7, litter 3).—Longitudinal section of the left (hypertrophied) kidney, showing the relative development of the cortex and the medulla.

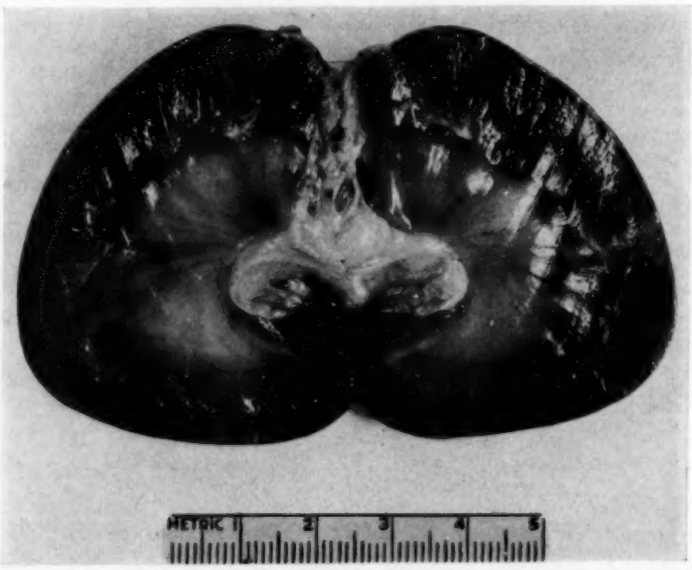

Fig. 3 (animal 8, litter 3).—Longitudinal section of the left, partially resected (hypertrophied) kidney, showing the relative development of the cortex and the medulla. The cortex near the site of resection (upper pole) is thickened.

20.6 per cent) and in those of litter 1 (37.9, 3.6, 8.45 and 5.55 per cent), as shown in table 3.

The gross appearance of the hypertrophic kidneys of the animals of litter 1 (fig. 1) shows that in puppies of this age (5 months or more) restoration of the normal renal contour does not occur, but, perhaps as a result of hypertrophy, a certain degree of bulging and rounding out of the surface is evident. A longitudinal section (figs. 2 and 3) shows that the cortex near the site of resection was noticeably thicker than elsewhere.

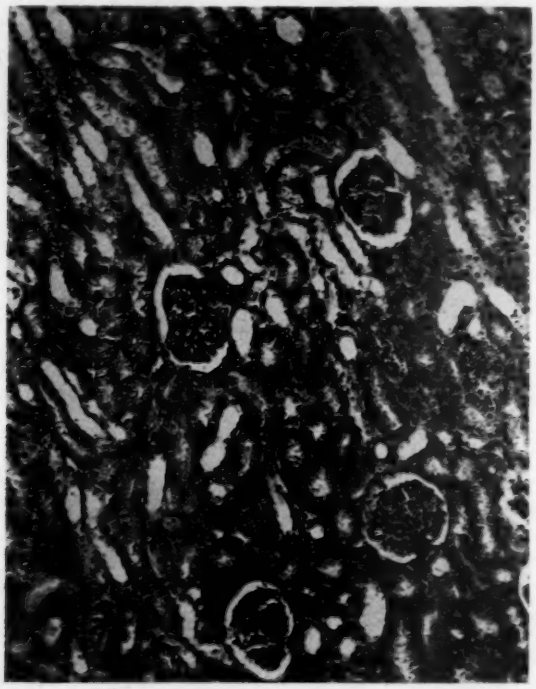

Fig. 4 (animal 4, litter 1).—Photomicrograph of a section of the cortex of the left kidney (upper pole), showing normal corpuscles and tubules at the start of the experiment (× 100).

Slight but perceptible differences of the same nature were observed in all the specimens which had been submitted to a partial resection.

Histologic studies of the renal cortex in various stages of hypertrophy (figs. 4, 5 and 6) demonstrated the differences in size of the renal corpuscles and convoluted tubules, as the experiment (litter 1) progressed and the hypertrophy became more marked. No evidence of new formation of glomeruli was seen. Mitotic figures indicating active cellular growth were numerous. Also, the highly vascular state, engorged

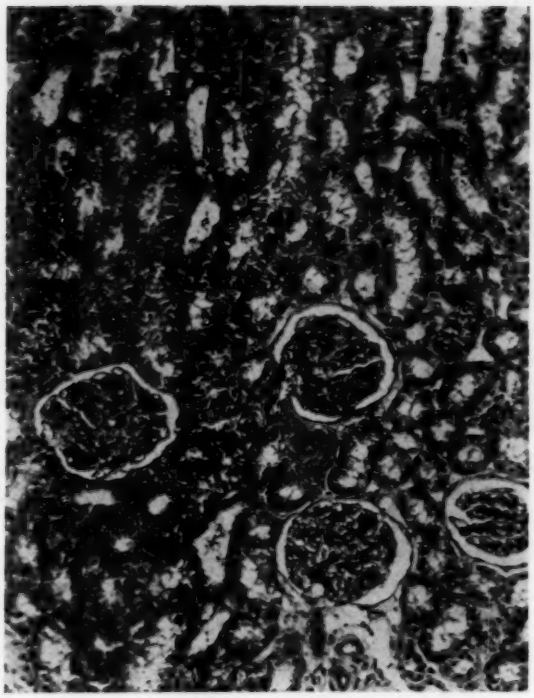

Fig. 5 (animal 4, litter 1).—Photomicrograph of a section of the cortex of the left kidney (lower pole) taken twenty-five weeks after the first resection, showing hypertrophic changes (× 100).

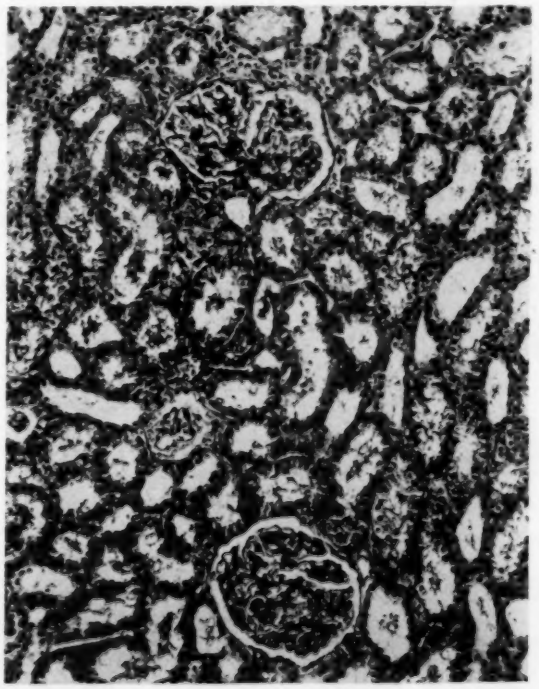

Fig. 6 (animal 4, litter 1).—Photomicrograph of a section of the cortex of the remaining segment of the left kidney seventy weeks after the first resection, showing marked hypertrophy (× 100).

capillaries and small vessels of the hypertrophic tissue were impressive. The glomerular tufts uniformly were filled with blood.

The fact that resection of the larger fractions of renal tissue, up to, roughly, two thirds of the renal substance, resulted in a greater response by hypertrophy of the remaining renal substance suggests that the response is a physiologic or work hypertrophy. This theory has been strengthened by other experiments which will be reported in later communications.

SUMMARY AND CONCLUSIONS

A series of eight dogs, aged from 5 to 6 months (one litter of four and two litters of two animals each) were subjected to resection of large fractions of renal substance; the largest fraction was not less than three fourths. After an interval of several months the degree and nature of the hypertrophic response of the remaining renal tissue were studied, and comparisons of the response in different animals of a litter were made.

Transitory increases occurred in the concentration of blood urea following resection, but as little as one fourth of the renal substance was capable of maintaining a normal concentration.

Readings of the blood pressure, made by indirect and by direct methods, were normal.

In one animal nearly three fourths of the renal substance (72.8 per cent) was removed at one operation, and the animal survived.

In another animal somewhat more than three fourths of the renal substance was removed in two stages by waiting for compensatory hypertrophy to occur in the interval, and the animal survived.

Evidence is presented which indicates that the larger the proportion of total renal substance resected (but not in excess of approximately 70 per cent) the greater is the relative hypertrophy which occurs, both in terms of the mass of the kidney and in terms of the size of the renal corpuscles and tubules.

These observations suggest that compensatory renal hypertrophy is a physiologic or work reaction.

PERIAPPENDICITIS WITHOUT APPENDICITIS

A STUDY BASED ON 26,051 APPENDIXES

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Periappendicitis unaccompanied by, or in marked excess of, inflammation in the appendix proper, has been noted frequently in the diagnostic services of the Pathological Laboratories of the University of Michigan. The possible clinical significance attaching to this condition, which has always been interesting from the pathologic standpoint, appeared to justify an analysis of the entire appendical collection in this laboratory.

LITERATURE

The literature on periappendicitis is much less abundant than one might expect. There are two chief standpoints from which the subject has been approached. One of these has to do with the relationship between appendicitis and inflammation of the female pelvic organs; the other, with the extraordinary susceptibility of the child to severe periappendical reaction to appendicitis proper. The several excellent monographs devoted to the appendix and its diseases (Aschoff,[1] Kelly and Hurdon,[2] Deaver,[3] Royster,[4] Sprengel [5]) treat of periappendicitis as a diagnostic problem, with scant attention to the pathologic peculiarities.

A. Lapthorn Smith [6] found seven "diseased appendices in about 100 patients operated on for pus tubes." He did not examine the appendixes microscopically. Downes [7] blamed failure of appendectomy to relieve symptoms in females on the fact that the primary seat of the disease was in the pelvis rather than in the appendix. Vineberg [8] commented on the frequent association of appendicitis and pelvic inflammation in females. In some instances he held the appendix primarily responsible; in others he was unable to establish a positive causal sequence. Duehrssen [9] removed 9 of 10 diseased appendixes in the course of 320 gynecological operations. Eight of the appendixes showed inflammation secondary to inflamma-

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From the Department of Pathology, University of Michigan; Carl V. Weller, director.

1. Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908.

2. Kelly, H. A., and Hurdon, E.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders Company, 1905.

3. Deaver, J. B.: Appendicitis, Philadelphia, P. Blakiston's Son & Co., 1914.

4. Royster, H. A.: Appendicitis, New York, D. Appleton & Company, 1927.

5. Sprengel, O.: Appendicitis, Stuttgart, Ferdinand Enke, 1906 (forms pt. 46d of Deutsche Chirurgie).

6. Smith, A. L.: Brit. M. J. **2**:1071, 1897.

7. Downes, A. J.: St. Louis M. & S. J. **82**:28, 1902.

8. Vineberg, H. N.: M. Rec. **57**:948, 1900.

9. Duehrssen, A.: Arch. f. klin. Chir. **59**:921, 1899.

tion of the pelvic organs. Hermes [10] found the appendix involved in 41 of 75 patients operated on for gynecological conditions. In most of these he considered the appendicitis secondary to the pelvic inflammation. Moritz [11] offered histologic evidence in proof of the opinion that the appendix was affected secondarily in 14 of 27 patients with oophoritis or salpingitis. On the other hand, she found the reverse relationship—perisalpingitis secondary to appendicitis—in only 1 of 44 patients whose oviducts and appendixes were available for examination. Anspach [12] and Polak [13] also declared appendical involvement to be secondary to tubal inflammation.

Graves,[14] however, stated that "severe inflammation of the tubes does not exhibit a special tendency to implicate the appendix, the result, doubtless, of gravity, which is effective in keeping the inflammatory products in the posterior and lower part of the true pelvis." Moreover, Graves suggested that appendicitis may be a frequent cause of salpingitis, spread of infection being, in this instance, favored by the forces of gravity. He did not consider the appendiculo-ovarian ligament of Clado an important factor in conveying inflammation from the fallopian tube and ovary to the appendix, because of the inconstant presence of this peritoneal fold. This belief is now generally shared. In "Nelson Loose Leaf Surgery" [15] it is stated that appendicitis secondary to pelvic inflammatory disease usually runs a self-limited course, without danger of morbidity or mortality.

Bland-Sutton [16] and Walker [17] each reported a case of a patient operated on for abdominal pain, with salpingitis secondary to appendicitis. Curtis [18] commented on the frequent association of appendicitis with salpingitis, but stated that this was a complication calling for emergency operation on only two occasions during a period of fifteen years. Counseller [19] considered the association of appendicitis and salpingitis not alarming. He believed that inflammation of either organ was capable of spreading to the other.

Deaver and Ravidin [20] were unable to determine, in some of their cases, whether the initial lesion was in the appendix or in the pelvic organs. They cited Waegeli as believing the appendix to be secondarily involved in 16.4 per cent of 896 women on whom laparotomies were done for gynecological diseases.

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10. Hermes, O.: Deutsche Ztschr. f. Chir. **50**:444, 1899; **68**:191, 1903.

11. Moritz, Eva: Ztschr. f. Geburtsh. u. Gynäk. **70**:404, 1912.

12. Anspach, B. M.: Gynecology, Philadelphia, J. B. Lippincott Company, 1927.

13. Polak, J. O.: Pelvic Inflammation in Women, New York, D. Appleton & Company, 1921.

14. Graves, W. P.: Gynecology, Philadelphia, W. B. Saunders Company, 1920.

15. Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1928, vol. 7, p. 13.

16. Bland-Sutton, J.: Brit. M. J. **2**:118, 1915.

17. Walker, A. T.: Am. J. Obst. & Gynec. **26**:448, 1933.

18. Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 2, p. 508.

19. Counseller, V. S., in Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 3, p. 704.

20. Deaver, J. B., and Ravidin, I. S.: Arch. Surg. **6**:31, 1923.

Pankow [21] found the appendix involved from without in 3.33 per cent of his material, but did not offer proof of the origin of the infection. Schridde [22] saw perisalpingitis secondary to appendicitis in only 6 of 286 patients. He believed the reverse relationship more frequent. McRae [23] attributed the reported higher incidence of appendicitis in males to mistaken diagnoses of conditions in females and conveyed the impression that the route of invasion is more often from the appendix to the oviduct than vice versa, as did also Ochsner [24] and Deaver.[25]

Hofmann [26] recently expressed himself as in doubt as to the exact sequence of infection when appendicitis and salpingitis are concurrently present. While Royster [4] considered the question still open, he found appendicitis as a complication of salpingitis on the right side in 66.6 per cent of his cases. He did not "regard salpingitis as so frequently resulting from infection of the appendix, if, indeed, it ever truly happens." He quoted Hayes, who found appendicitis present as a complication in 71 per cent of cases of acute salpingitis at the State University Hospital in Oklahoma City.

Much of the aforementioned discussion, however, could have been obviated by careful routine histologic examination of the organs removed.

As will appear later, appendixes removed from children play an important rôle in this study. "Spreading peritonitis" as a complication of appendicitis in children receives frequent mention in the literature. Aschoff [27] stated that the serosa of the appendix often shows a toxic noninfectious inflammatory process following a "primary lesion" of appendicitis. This peritonitis usually involves the distal portion of the appendix and is especially common in young people. Hudson [28] and Lipshutz [29] stressed the high mortality of appendicitis in childhood because of the spread of infection. Kirschenmann [30] found free fluid in the abdomen and a swollen, congested appendix during the early stages of acute appendicitis in children, before the occurrence of suppuration.

McCosh [31] remarked on the insidious course of appendicitis in children, with its special tendency to cause peritonitis. He suggested that this may be due to the inability of the peritoneum to wall off the inflammation as readily in children as in adults. Churchman [32] stated that appendicitis in children is distinguished from that in adults by a greater tendency to perforation and the more frequent occurrence of spreading peritonitis. In a recent paper, Maes, Boyce and McFettridge [33] also commented on the special dangers of appendicitis in children.

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21. Pankow, O.: Beitr. z. Geburtsh. u. Gynäk. **13**:50, 1909.

22. Schridde, H.: Die eitrigen Entzündungen des Eileiters, Jena, Gustav Fischer, 1910.

23. McRae, F. W.: New York M. J. **73**:189, 1901.

24. Ochsner, A. J.: J. A. M. A. **33**:192, 1899.

25. Deaver, J. B.: J. A. M. A. **33**:197, 1899.

26. Hofmann, H.: Monatschr. f. Geburtsh. u. Gynäk. **93**:377, 1933.

27. Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1928, vol. 2, p. 784.

28. Hudson, H. W.: New England J. Med. **207**:255, 1932.

29. Lipshutz, B.: Arch. Pediat. **48**:649, 1931.

30. Kirschenmann, J. J.: Am. J. Surg. **16**:318, 1932.

31. McCosh, A. J.: J. A. M. A. **43**:853, 1904.

32. Churchman, J. W.: Bull. Johns Hopkins Hosp. **20**:31, 1909.

33. Maes, U.; Boyce, F. F., and McFettridge, E. M.: Surg., Gynec. & Obst. **58**:32, 1934.

I have not been able to find any reports giving the actual or the comparative incidence of periappendicitis following appendicitis at various age periods or in the two sexes. It may, however, be inferred that periappendicitis constitutes a special clinical problem in women and in children. In the following section it will be shown that this clinical inference is fully substantiated by the pathologic observations.

MATERIAL AND METHODS

This material consists of 26,051 appendixes received for routine diagnosis at the Pathological Laboratories of the University of Michigan during the period from July 1, 1894, to Oct. 31, 1932.[34] Only surgical specimens are included. Most of these appendixes came from residents of Michigan and were removed in the University Hospital and in other hospitals distributed over the State.

The specimens were received in 10 per cent solution of formaldehyde. Since 1903, as a routine measure, blocks have been taken to include representative portions of the proximal, middle and distal thirds, while prior to that period the organ was sectioned at but one or two levels. When indicated, blocks were taken at four or more levels. Duplicate sections were usually prepared, but serial sections were made only when specially indicated. With few exceptions, the diagnoses were rendered by the directors of the laboratories, Dr. A. S. Warthin and Dr. C. V. Weller.

For the purposes of this study, all appendixes the lesions of which had been diagnosed as periappendicitis without appendicitis or periappendicitis in excess of the appendicitis were assembled and reexamined, special attention being paid to the location, distribution and character of the exudate. Note was made, also, of concomitant changes in the appendix proper. As a preliminary study, representative appendixes removed from children, adult males, adult females with healthy oviducts and adult females with histologically proved salpingitis were examined with a view to comparing and contrasting the lesions found. A final study was then made of the entire material, and the data were recorded without reference to the sex and age of the patients, or the conditions present in the accompanying organs. When judgments as to the pathologic changes present had been entered, additional items relating to age, sex and involvement of other viscera were assembled.

INCIDENCE OF DISPROPORTIONATE PERIAPPENDICITIS

Periappendicitis disproportionate to the pathologic condition in the interior of the organ was found in 1,483 of the 26,051 appendixes (5.69 per cent). Pertinent data relating to the distribution of all the appendixes and of those showing periappendicitis in relation to age and sex are presented in table 1.

With regard to the general incidence, disproportionate periappendicitis occupies an important place among pathologic involvements of the appendix at all age periods. A paucity of material from patients aged 2 years or less renders the data for the first age division statistically

34. The latter date is chosen to make the statistics reported in this paper fully comparable with those presented in a previous study directed along entirely different lines (Gordon, H.: Arch. Path. **16**:177, 1933).

unreliable. During the period from birth to 6 years, the incidence of disproportionately severe periappendicitis is 6 per cent. It then drops to 3.4 per cent in the next quinquennium, only to rise abruptly to its maximum of 7.7 per cent in the period from 17 to 21 years. It then falls gradually until after the fifth decade, when this type of periappendicitis is no longer a frequent finding.

A more informative study is afforded by segregating the figures for each sex. In boys up to 6 years of age, the incidence of disproportionate periappendicitis is 5 per cent. The incidence is 3.4 per cent in

TABLE 1.—*Distribution of Entire Material as to Age, Sex and Presence of Disproportionate Periappendicitis*

	Males and Females			Males			Females		
		Cases of Periappendicitis*			Cases of Periappendicitis			Cases of Periappendicitis	
Age Period	Appendixes	Number	Percentage	Appendixes	Number	Percentage	Appendixes	Number	Percentage
Not stated.....	10,467	661	6.3	3,521	49	1.4	6,826	604	8.8
Birth to 23 mos.	18	3	16.6	11	2	18.1	6	1	16.1
2- 6 years.....	298	16	5.4	186	8	4.3	111	8	7.2
7-11 years.....	811	28	3.4	409	14	3.4	401	14	3.5
12-16 years.....	1,696	65	3.8	603	7	1.1	1,093	58	5.3
17-21 years.....	3,011	233	7.7	1,083	17	1.5	1,925	215	11.2
22-26 years.....	2,732	184	6.8	1,012	9	0.9	1,720	175	10.1
27-31 years.....	2,044	119	5.8	756	7	0.9	1,287	112	8.7
32-36 years.....	1,582	68	4.3	552	5	0.9	1,028	63	6.1
37-41 years.....	1,110	44	3.9	430	5	1.1	678	38	5.6
42-46 years.....	859	26	3.0	323	3	0.9	536	23	4.3
47-51 years.....	591	24	4.0	240	1	0.4	350	23	6.6
52-56 years.....	398	6	1.5	156	1	0.7	240	5	2.1
57-61 years.....	220	2	0.9	87	0	0.0	133	2	1.5
62-66 years.....	130	2	1.5	60	0	0.0	68	2	2.9
67-71 years.....	50	1	2.0	20	0	0.0	29	1	3.4
72 and over.....	34	1	2.9	22	1	4.5	11	0	0.0
Total.....	26,051	1,483	5.6	9,471	129	1.3	16,442	1,344	8.1

* Throughout this table and tables 2 and 3 "periappendicitis" refers to "disproportionate periappendicitis."

the group from 7 to 11 years of age. From the twelfth year on, periappendicitis occurs with surprising uniformity, the incidence varying little from 1 per cent. In females, on the contrary, there is a relationship to age altogether different from that found in males. In the period from birth to 6 years of age, disproportionate periappendicitis shows an incidence of 7.7 per cent. In the group from 7 to 11 years of age, the incidence drops to 3.5 per cent, which is practically identical with that for boys at this age, but then rises rapidly to attain its maximum (11.2 per cent) in the group from 17 to 21 years of age. The figures then show a gradual decrease until the beginning of the fifth decade. Contrasting the figures for the two sexes, it is evident that the basic

incidence of periappendicitis in males, after childhood, is approximately 1 per cent. Superimposed on this basic incidence in females, there is a secondary wave of incidence intimately linked with age. This sex-age incidence and relationship is especially striking when expressed graphically (fig. 1).

If for each age period the percentage incidence of disproportionate periappendicitis in females be divided by the percentage incidence of disproportionate periappendicitis in males, a series of indexes is obtained which expresses the relative incidence, fully weighted, for the varying amounts of material in the two sexes. These indexes are shown in the final column of table 2 and may be interpreted as follows: A value less than unity indicates a higher incidence in males than in females at a given age period; unity indicates an equal incidence in the two sexes, and

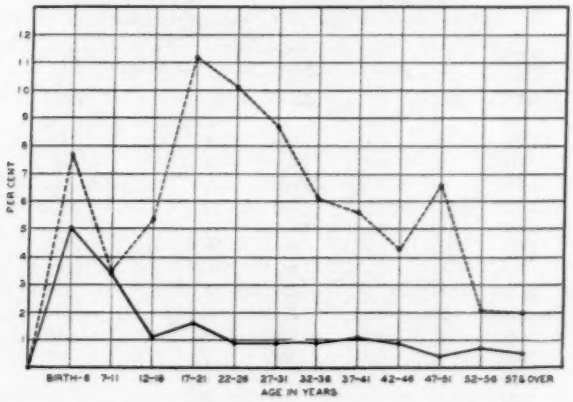

Fig. 1.—The percentage incidence of disproportionate periappendicitis for males and for females by age groups. Disproportionate periappendicitis in males is represented by the solid line, and that in females by the broken line.

a value greater than one indicates a preponderance in females. The relationship of these values is shown in figure 2.

From these indexes it becomes all the more evident that a fundamentally equal incidence of disproportionate periappendicitis in males and females is overlaid by a marked preponderance of incidence in females which begins with the potential sexual life of the female and reaches its most effective level in the group from 22 to 26 years of age. This period of increasing incidence confined to females is the very period in which salpingitis is common. It is not so easy to find a satisfactory explanation of the sharp rise of the index in the group from 47 to 51 years of age, indicating a great preponderance of disproportionate periappendicitis in females. One important factor which elevates the index is the very low incidence in men at this age. As a matter of fact, the percentage incidence in the female, as shown in table 1, is

higher by only 2.3 than in the preceding five years. This moderate increase may well be explained by the fact that the discomforts incident to the menopause may increase the number seeking medical advice, thus leading to the discovery of a greater number of conditions requiring surgical intervention. Patients believed to be suffering from the residual effects of pelvic inflammatory disease must constitute an important part of the operative material at that age.

PATHOLOGIC CLASSIFICATIONS OF PERIAPPENDICITIS

Periappendicitis may be classified as periappendicitis with comparable appendicitis and periappendicitis without comparable appendicitis.

TABLE 2.—*Corrected Indexes of Relative Incidence of Disproportionate Periappendicitis in Each Age Group*

$$\frac{\text{Percentage Incidence in Females}}{\text{Percentage Incidence in Males}} = \text{Corrected Index of Incidence for Each Age Group}$$

	Males			Females			
		Cases of Periappendicitis			Cases of Periappendicitis		Ratio:
Age Periods	Appendixes	Number	Percentage	Appendixes	Number	Percentage	% Incidence in Females / % Incidence in Males
Birth to 23 months..	11	2	18.1	6	1	16.6	0.9
2- 6 years.....	186	8	4.3	111	8	7.2	1.7
7-11 years.....	409	14	3.4	401	14	3.5	1.0
12-16 years.....	603	7	1.1	1,096	58	5.3	4.8
17-21 years.....	1,083	17	1.5	1,925	215	11.2	7.4
22-26 years.....	1,012	9	0.9	1,720	175	10.1	11.2
27-31 years.....	756	7	0.9	1,287	112	8.7	9.6
32-36 years.....	552	5	0.9	1,028	63	6.1	6.8
37-41 years.....	430	5	1.1	678	38	5.6	5.0
42-46 years.....	323	3	0.9	536	23	4.3	4.8
47-51 years.....	240	1	0.4	350	23	6.6	16.5
52-56 years.....	156	1	0.7	240	5	2.1	3.0
57 years and over...	189	1	0.5	241	5	2.0	4.0

The latter includes (1) a juvenile type (persistent after appendicitis proper has subsided) and (2) a type secondary to extra-appendical inflammation. The secondary type may depend on (1) pelvic inflammatory disease or (2) other inflammatory conditions.

Of periappendicitis accompanying severe purulent, suppurative or gangrenous appendicitis, little need be said. This type is thoroughly familiar to pathologists and clinicians and forms no part of the subject matter of this paper.

PERIAPPENDICITIS WITHOUT COMPARABLE APPENDICITIS

Juvenile Type.—As has been shown in the preceding survey of the literature, periappendicitis is especially severe in children, frequently disproportionate to the process in the mucosa; it oftentimes persists after the mucosal and submucosal inflammation has largely subsided.

As to the microscopic observations, individual appendixes vary slightly, but in general there is a well defined basic pattern in juvenile appendixes with disproportionate periappendicitis. The mucosa usually shows only some increase in goblet cells. The submucosa shows but slight inflammatory infiltration, usually by eosinophils. The lymphoid tissue varies within wide limits, but is often hyperplastic. In the muscularis propria there is a more obvious inflammatory exudate—eosinophils and basophils and some inflammatory edema. The cellular exudate may involve the entire thickness of the muscularis propria. In every instance, however, the serosa shows the most marked involvement (fig. 3). The exudate here consists of polymorphonuclear leukocytes—neutrophils

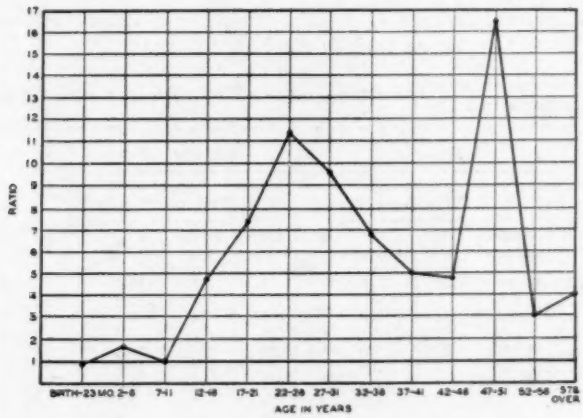

Fig. 2.—Graph of the corrected ratio of disproportionate periappendicitis in females to that in males, showing the marked preponderance of the incidence in females after the age of puberty.

and basophils—and fibrin in varying proportions. As a rule the fibrin is not abundant. The attached border of the meso-appendix is always involved and sometimes even shows miliary abscesses. The infiltration extends outward from the meso-appendix to involve the entire peritoneal surface of the appendix. The most constant and marked involvement, however, is at the angle of reflection between the appendix and its mesentery (fig. 4). The exudate was present at all levels available for examination in 36 of the 47 appendixes belonging to this group. In 5, while present at all levels, the inflammation appeared more severe at one or two of the three levels, and in 11 it was present at only one or two levels. In short, this type of periappendicitis is essentially the result of a fulminating or, in some cases, a neglected appendicitis which has largely subsided so far as the mucosa is concerned.

Periappendicitis Secondary to Pelvic Inflammatory Disease.—This is the form represented in the increased incidence of periappendicitis in females during the early part of the reproductive period and it is by far the most frequent type encountered in the present series. While not entirely pathognomonic, the pathologic picture is highly distinctive. The serosa of the appendix shows an active inflammatory process,

Fig. 3.—A boy, aged 4, had pain in the right lower quadrant of the abdomen for three and a half days, with vomiting and diarrhea. The section shows heavy fibrinopurulent exudate in the subserosa and over the serosa, and less marked purulent infiltration of the muscularis propria. The submucosa and mucosa were normal at the three levels examined. The juvenile type of periappendicitis was diagnosed. Hemalum and eosin stain; × 90.

often severe and sometimes extensive. The remaining coats of the appendix, on the contrary, show no noteworthy changes. There is an abundant leukocytic exudate with a scant admixture of fibrin in the acute phase (fig. 5). The exudate shows a predilection for accumulating

locally, especially along one surface of the meso-appendix close to its reflection from the appendix. On exploring the circumference of the appendix one finds a gradual attenuation of the exudate. But only in its earliest and simplest form is this a strictly localized inflammation. At a later stage the exudate frequently shows secondary accumulations along the circumference of the appendix. Some of these appendixes show a localized periappendicitis with the most abundant exudate at a

Fig. 4.—A boy, aged 7, "came home from school with pain and vomiting." Operation was immediate. The section shows a heavy collection of leukocytes and fibrin at the angle of reflection of the meso-appendix and purulent infiltration at the base and along the surface of the meso-appendix. The muscularis propria is less severely involved. The mucosa was normal at all levels examined. The juvenile type of periappendicitis was diagnosed. Hemalum and eosin stain; × 35.

point almost exactly opposite the meso-appendix (fig. 6 *A*). A lesser number show spread of the exudate along both surfaces of the meso-appendix, reaching a short distance along the circumference of the appendix. As is to be expected from the etiology predicated for this

condition, the distal and middle portions are involved more frequently and more severely. A few of the appendixes show localized strands of adhesions (usually opposite the meso-appendix) with but little active inflammation. In some, there is a hyperplasia of the rudimentary lymphoid follicles along the surface (fig. 6*B*). In the older examples there are many plasma cells in the inflammatory exudate.

This type of periappendicitis in its inception is essentially a localized process. The meso-appendix shows no infiltration of its attachment

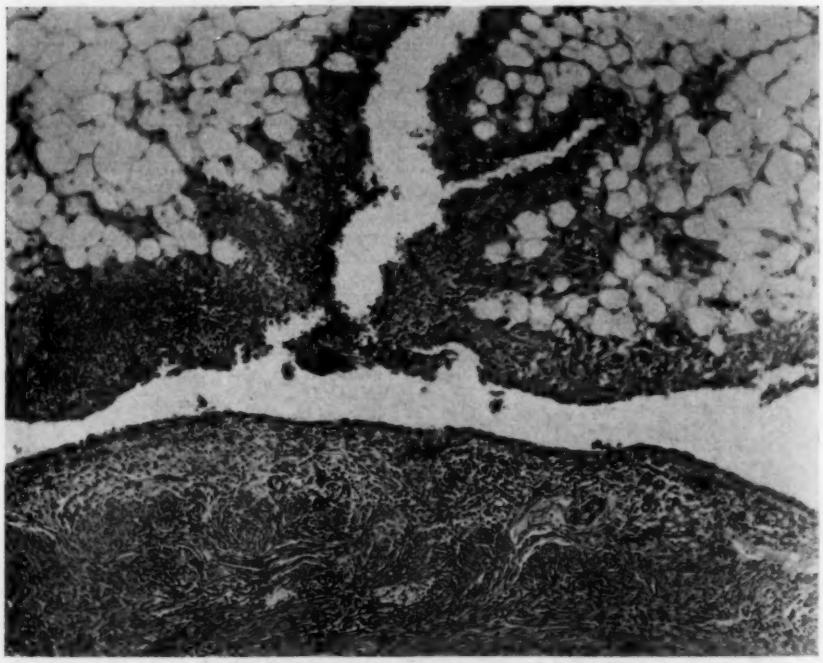

Fig. 5.—A woman, aged 30, had "sudden cramp-like pains over the lower part of the abdomen; the pain lasted a few days and then shifted to the right." There was tenderness in the left lower quadrant of the abdomen, and the patient had fever. The section shows purulent inflammation of the meso-appendix; the muscularis propria is unaffected. The mucosa and submucosa were normal except for an old obliteration of the tip of the appendix. The oviducts were removed at the same time and showed a severe acute purulent salpingitis and perisalpingitis. Acute purulent periappendicitis was diagnosed. Hemalum and eosin stain; × 90.

and only superficial involvement of its substance. There is nothing in the appendix itself to account for the inflammation.

In the present series, the oviducts were available for examination from 862 of the 1,321 adult female patients (table 3). Of these patients, 841 showed an active purulent salpingitis; 5, tubal gestation; 5, tuber-

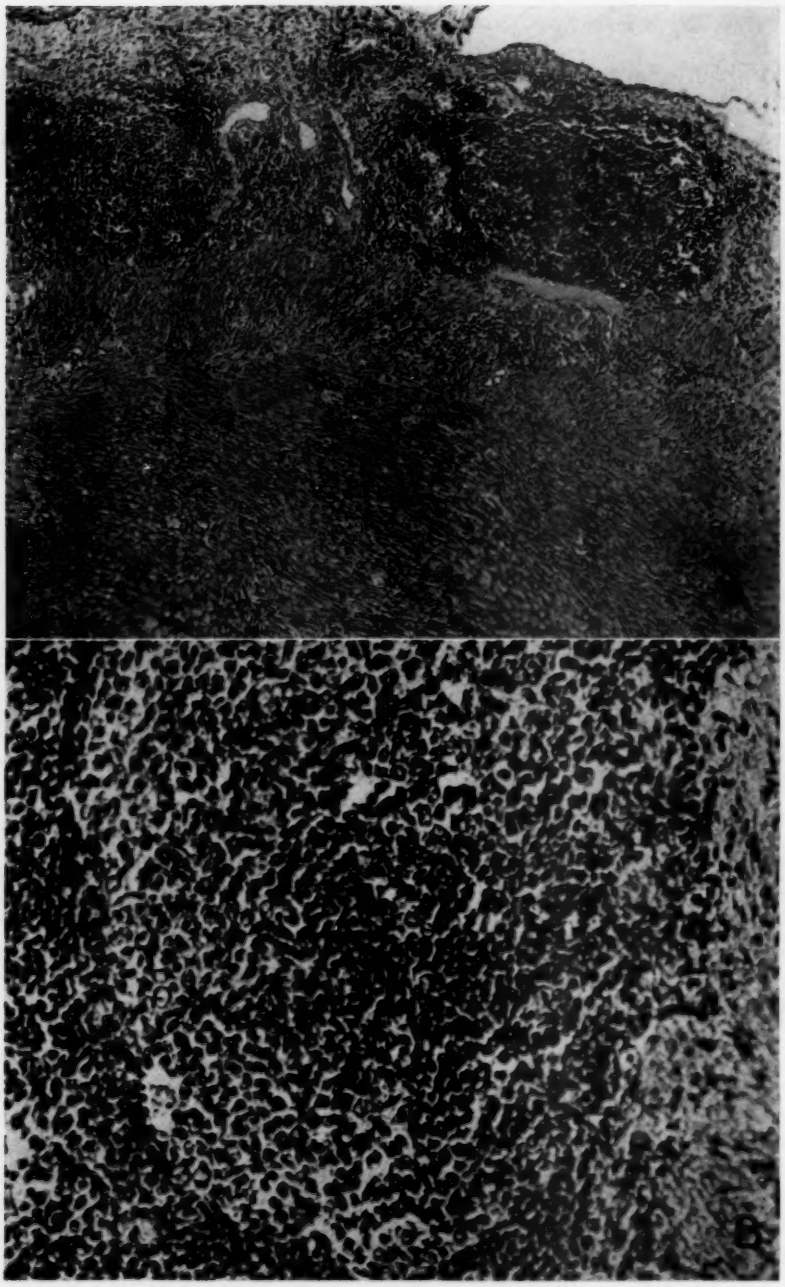

Fig. 6.—A woman, aged 24, had inconstant pain on the right side for six weeks, which was more severe during menstruation. Section *A* shows the serosa much thickened and shows hyperplasia of the rudimentary lymphoid follicles, as well as diffuse lymphocytic infiltration; the muscularis propria is unaffected. The mucosa and submucosa were normal at the three levels sectioned. The fallopian tubes showed severe purulent salpingitis. Section *B* shows one of the lymphoid follicles under higher magnification. Periappendicitis secondary to salpingitis was diagnosed. Hemalum and eosin stain; *A*, × 120; *B*, × 250.

culous salpingitis. The fallopian tubes in 11 patients were normal, and those in 459 were not removed. Thus it is seen that, when the tubes were available for examination, only 1.27 per cent were normal, whereas 98.1 per cent showed purulent salpingitis in association with the periappendicitis. It may be argued that this is selected material, since these oviducts were removed because they were diseased. This objection, however, does not lessen the significance of the coincidence of the two conditions.

The 459 adult females with disproportionate periappendicitis whose oviducts were not available for examination included a group of 143 in whom the periappendicitis was considered probably not secondary to salpingitis or other pelvic inflammations. This group of 143 showed appendical pathologic conditions similar to those occurring in males.

TABLE 3.—*All Examples of Disproportionate Periappendicitis Grouped as to Degree and in Relation to Significant Clinical Data*

Group	Condition of Fallopian Tubes	Degree of Periappendicitis: Very Severe	Moderately Severe	Moderately Severe	Moderately Slight	Adhesions Only	Total
Adult females from whom fallopian tubes were available for examination	Purulent salpingitis	41	157	254	294	95	841
	Tubal pregnancy	0	0	2	2	1	5
	Tuberculous salpingitis	0	0	1	1	3	5
	Tubes normal	0	1	2	6	2	11
Adult females from whom fallopian tubes were not received		25	113	155	97	69	459
Adult males		6	22	30	30	17	105
Juvenile females		3	5	5	10	0	23
Juvenile males		10	10	0	2	2	24
Sex not stated		0	1	3	1	5	10
Totals		85	309	452	443	194	1,483

They may be considered as showing periappendicitis secondary to appendicitis, or periappendicitis secondary to other forms of peritonitis. This leaves a further group of 319 in whom the periappendicitis may presumably be attributed to salpingitis or other pelvic inflammations, although with less certainty than in the larger group in whom the oviducts were available for examination. On combining these groups, it appears that 1,162 of the 1,321 examples of disproportionate periappendicitis in adult females, i. e., 87.9 per cent, either were actually associated with a known salpingitis or may conservatively be assumed to have been so associated. These figures are the more striking because of the size of this material, its unselected nature and the length of time during which it has accumulated.

Periappendicitis Secondary to Miscellaneous Inflammatory Conditions.—This type of disproportionate periappendicitis may occur in either males or females and at any age period, but is somewhat more common after the thirtieth year. A paucity of clinical data prohibits

a positive statement as to the relative sex incidence. In this group, again, the mucosa of the appendix shows neither ulceration nor active infiltration. The submucosa often shows an old fibrosis and occasionally some eosinophil infiltration. The muscularis propria is often thickened, usually owing to the presence of hyaline connective tissue. The serosa shows an active purulent or fibrinopurulent inflammation (fig. 7). The

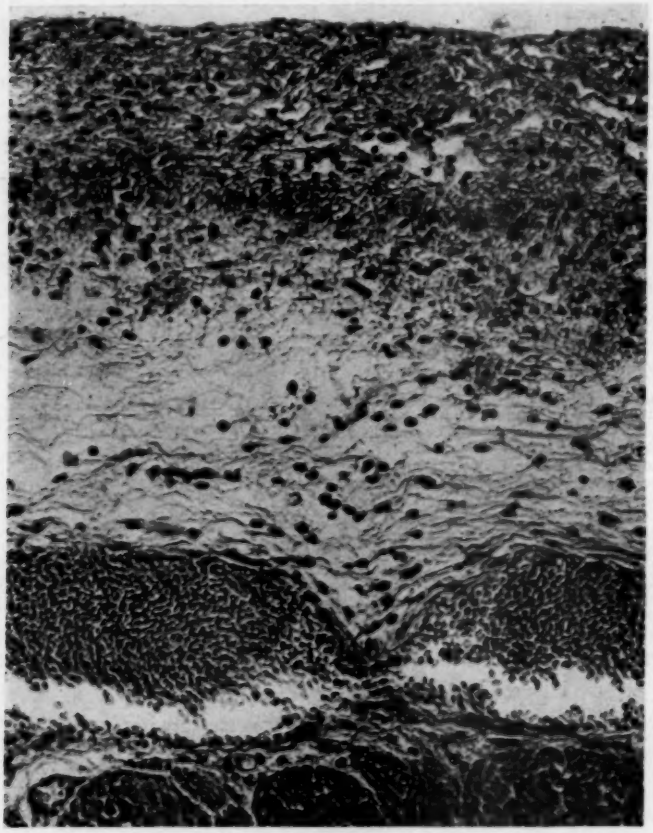

Fig. 7.—A man, aged 39, had severe subacute fibrinopurulent periappendicitis of the type which is secondary to inflammation elsewhere in the peritoneum. The section reveals inflammatory thickening of the serosa. There was an old partial obliteration of the appendix. No evidence of active appendicitis was seen at the four levels examined. Hemalum and eosin stain; × 120.

exudate is usually present at all levels available for examination but not to an equal extent. The infiltrations do not extend any distance beneath the peritoneal surface, and the meso-appendix shows no involvement of its substance. The point of maximum intensity of the exudate

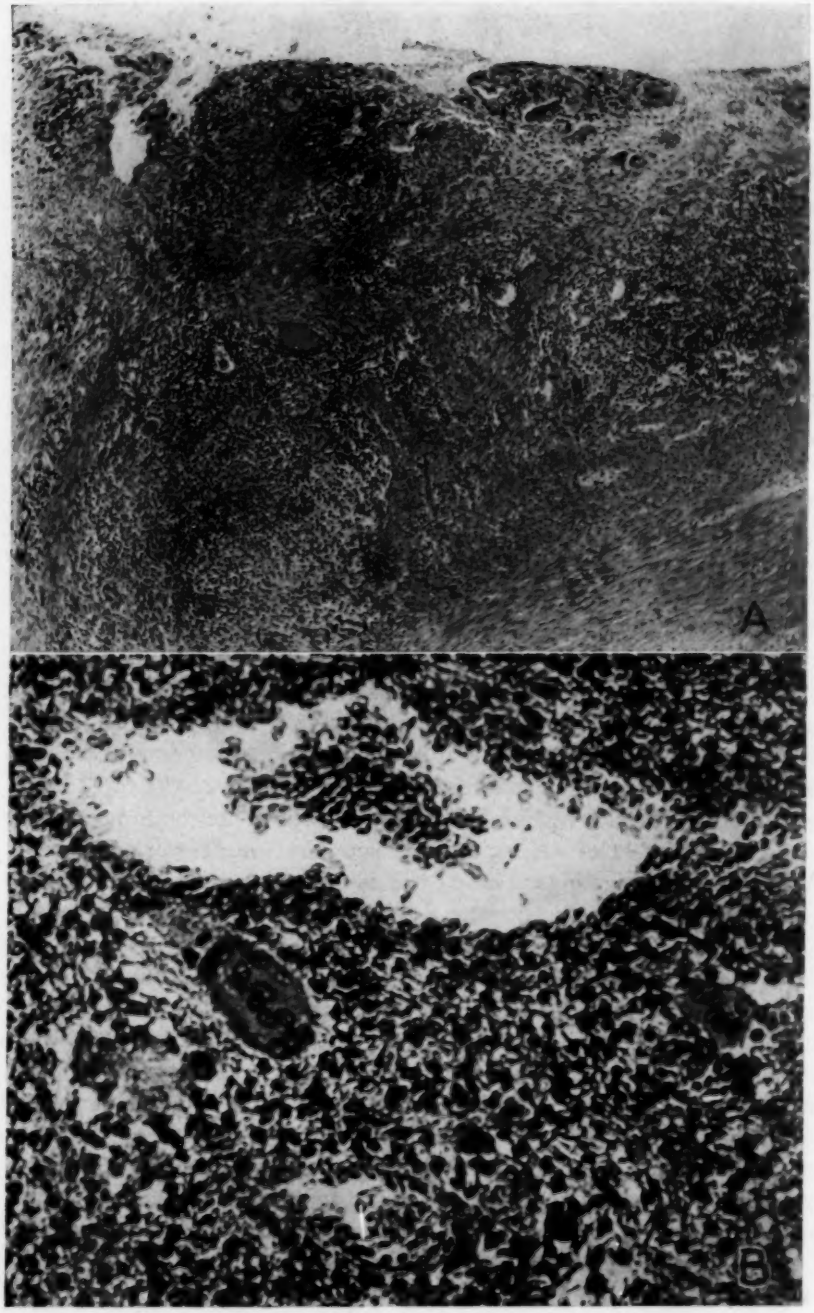

Fig. 8.—A man, aged 21, had a clinical diagnosis of "peritonitis following injury." Section *A* shows active chronic productive periappendicitis with masses of vascular granulation tissue and numerous foreign body pseudotubercles. Section *B* shows foreign body giant cells, one of which contains partly absorbed foreign material. Hemalum and eosin stain; *A*, × 90; *B*, × 300.

varies; it usually shows a marked accumulation at the angles of reflection between the meso-appendix and the appendix. In essence, this is merely part of a generalized peritonitis, such as may be due to any of the intra-abdominal causes of peritonitis other than appendicitis. If the pathologist has only the appendix available, it is seldom possible to determine the etiology. Under special circumstances, however, the character of the exudate or of the granulation tissue may reveal the cause (fig. 8).

COMMENT

In view of the findings reported here, it seems remarkable that similar studies are not available in the literature. A large part of the responsibility for the lack of such data must rest with the pathologist.

Periappendicitis of the juvenile type, while apparently familiar to clinicians, does not figure directly in the pathologic classifications made by the authors quoted. The explanation of this type is still uncertain. I agree with Maes, Boyce and McFettridge,[33] who refuse to accept unreservedly the explanations commonly advanced: the delicate walls and excess of lymphoid tissue of the child's appendix as compared with that of the adult. It is more likely that a considerable part of the incidence of juvenile periappendicitis can be attributed to what these authors, paraphrasing Moynihan, so aptly call "purgation, procrastination and then perforation." But the appendixes of some children, despite the most commendably prompt operative intervention, still show periappendicitis much in excess of the appendicitis. In these the inflammation is probably of a fulminating character from its very inception. Aschoff's [27] investigations pointing to a toxic noninfectious inflammation of the peritoneum are pertinent.

With regard to disproportionate periappendicitis secondary to salpingitis, the controversial points raised in the literature could in large measure have been avoided by systematic histologic study of the material. In the diagnostic service with which I am associated, undoubted examples of salpingitis secondary to appendicitis have been seen; and the sequence can usually be established with little room for doubt. In these instances, the appendix shows an active—and usually severe—inflammation of all its coats. This inflammation tends to be older than the inflammation in the oviducts. The right fallopian tube, less often the left, commonly shows perisalpingitis rather than salpingitis. The plications do not show the severe cellular infiltrations usually seen in acute salpingitis. In the service with which I am associated, the oviducts are always examined at, at least, two well separated levels. In true salpingitis all levels show, at least in the early stages, an equally severe inflammation. In perisalpingitis secondary to appendicitis, it is chiefly the fimbriate or the ampullary portion which shows infiltration of the

mucosa. Even at these levels the mucosal involvement is not severe and is of a lesser degree than the involvement of the outer coats of the tube. Appendicitis is probably far less seldom mistaken for salpingitis than vice versa. The appendix is therefore apt to be removed before there is time for the inflammation to spread to the pelvic organs. On the other hand, it is considered good clinical practice to delay operation for salpingitis until the acute phase has subsided. This delay favors spread of the inflammation from the oviduct to the outer coat of the appendix. On the basis of the findings in the present series, I cannot substantiate Graves [14] in his conclusion that severe inflammation of the fallopian tubes does not commonly involve the appendix. Moritz [11] reported a predominance of plasma cells in the exudate of periappendicitis secondary to salpingitis of gonococcic origin. My material, on the other hand, does not entirely substantiate this observation. While plasma cells were plentiful in the periappendical exudate of some of the patients with salpingitis, others showed a decided preponderance of lymphocytes. In some instances, numerous hyperplastic rudimentary lymphoid nodules, such as have been considered as indicating a gonococcic etiology in the cervix, prostate and fallopian tubes, were encountered (fig. 6). Bacteriologic proof by cultural methods has been prevented by routine fixation of the material in dilute solution of formaldehyde before its receipt.

Recognition by the pathologist of periappendicitis secondary to salpingitis is important because it enables him to warn the surgeon of the existence of another and primary focus of inflammation. Oftentimes the appendix is removed through an incision so small that the surgeon cannot examine other abdominal viscera. The pathologist's warning makes it possible for the surgeon to anticipate complications that will lead to protracted convalescence, and permits him to prepare those interested in the patient for the fact that her operation cannot be expected to relieve the signs and symptoms in their entirety.

Little more need be said of disproportionate periappendicitis secondary to miscellaneous inflammatory conditions in the abdomen. The number of cases of this condition in any series will vary according to the clinical judgment of the surgeons. Some of the appendixes in the present series were undoubtedly removed as a prophylactic measure during the course of exploratory laparotomies or other intra-abdominal operations. In these, the surgeon must have been aware of the presence of generalized peritonitis, of which the periappendicitis was merely a part.

CONCLUSIONS

Periappendicitis disproportionate to the appendicitis, or periappendicitis without appendicitis, occurred in 1,483 of 26,051 appendixes (5.69 per cent).

Disproportionate periappendicitis may be classified, as to pathogenesis, into a juvenile type, a type following pelvic inflammation and a type secondary to miscellaneous inflammatory conditions.

Disproportionate periappendicitis in juvenile patients is due to delay in undertaking operation or to fulminating appendicitis, and occurs with about equal frequency in males and females.

In the entire series disproportionate periappendicitis occurs six times as frequently in females as in males. This increased incidence in females is most evident during and after adolescence.

In females, salpingitis is the most common cause of disproportionate periappendicitis.

In males, disproportionate periappendicitis is due either to subsiding appendicitis or to inflammation elsewhere in the abdominal cavity.

Case Reports, Laboratory Methods and Technical Notes

A SO-CALLED ALVEOLAR CELL CANCER OF THE LUNG

HENRY C. SWEANY, M.D., CHICAGO

During the last few decades, there has been reported a marked increase in the intrathoracic tumors, particularly in those originating within the lungs and bronchi. Primary cancers of the lung were rarely reported before the discovery of the tubercle bacillus, and few even before the discovery of the x-ray. Reinhard [1] could find only 25 in 1878; Paessler,[2] 57 in 1896, and Adler,[3] 374 by 1912. Since then the reports number thousands. Hruby and Sweany [4] recently collected 2,359 such cancers from only part of the large collections.

The origin of primary cancers of the lung was not given much consideration until Waldeyer [5] in 1867 suggested that they began in the pulmonary epithelium. Langhans [6] in 1870, followed by Chiari,[7] Ebstein [8] and others, rendered reports of cases in which the tumors contained large numbers of mucus-bearing cells. From this they concluded that such tumors came from the mucous glands of the bronchi. As definite pavement epithelial tumors began to appear, Perls,[9] Fuchs,[10] Tillmann [11] and others ascribed their origin to the alveolar epithelium principally because of external appearances and perhaps because they were unable to find a definite point of origin elsewhere. Since then most of these tumors have been found to originate from the walls of the larger bronchi, and consequently the theory of the alveolar cell origin of these "pavement cell" forms was disproved. Nevertheless, there were certain types that still were compatible with an origin in the finer bronchioles or actually from the alveolar cells. Grünwald,[12] in 1885, presented reports of two such cases, and added another of his own. Kurt Wolf[13] in 1895, added one of his own and cited one of

From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

1. Reinhard, W.: Arch. f. d. Heilk. **19**:369, 1878.
2. Paessler, H.: Virchows Arch. f. path. Anat. **145**:191, 1896.
3. Adler, I.: Primary Malignant Growths of the Lung and Bronchi, New York, Longmans, Green & Co., 1912.
4. Hruby, A. J., and Sweany, H. C.: Arch. Int. Med. **52**:497, 1933.
5. Waldeyer, A.: Virchows Arch. f. path. Anat. **41**:470, 1867.
6. Langhans, T.: Virchows Arch. f. path. Anat. **53**:470, 1871.
7. Chiari: Prag. med. Wchnschr. **8**:497, 1883.
8. Ebstein, W.: Deutsche med. Wchnschr. **26**:921, 1890.
9. Perls, M.: Virchows Arch. f. path. Anat. **56**:437, 1872.
10. Fuchs, F.: Inaugural Dissert., Munich, 1886.
11. Tillmann, W.: Inaugural Dissert., Halle, 1889.
12. Grünwald: München. med. Wchnschr. **36**:548 and 566, 1889.
13. Wolf, K.: Fortschr. d. Med. **13**:725 and 765, 1895.

Fuchs' as another. Kretschmer,[14] in 1904, added still another. Pépère [15] described one in the same year that could not be differentiated grossly from pneumonia in the gray stage of hepatization. The cells were of a low columnar type in alveolar arrangement. Morelli,[16] in 1907, described an interesting specimen that may well be added to the list. Since then the emphasis on this group has not been so great. The chief points of difference between these cancers and other cancers of the lung are: the uniform cuboidal or low cylindric type of cell, the alveolar arrangement (actually supplanting the alveolar epithelium), and the homogeneous diffuse appearance (like the gray stage of lobar pneumonia). Although the interest in the group may be chiefly academic, it seems that there are certain features that may be of interest from the point of view of the histogenesis of tumors of the lung, about which there is still a divided opinion.

It has been fairly well established that the basal layer of the epithelium is the source of most cancers, as suggested by McCarthy,[17] Moise,[18] Freid [19] and others. The latter two have dealt especially with cancers of the lung. According to these men, the basal layer of epithelium is looked on as more of a semiembryonic type of cell with a multipotential nature, and in the course of a normal replacement resulting from injury these cells are sometimes not limited to the replacement of the destroyed tissue, but continue on as a malignant neoplastic growth. The majority of cancers of the lung can, therefore, be shown to originate from the basal layer of epithelium of the bronchi. There are a few who still hold that the mucous glands may become malignant, and this must be an admitted possibility in spite of the fact that the basal layer of epithelium may undergo metaplastic change to simulate bronchial mucous glands. The chief question regarding the origin of primary cancers of the lung today concerns the aforementioned types.

Obviously, the origin of these forms is narrowed down to two sources: the finer bronchioles and pulmonary alveoli. Without going any further into the theory at this point, I shall report a case with autopsy which presented an unusual type of pulmonary cancer.

REPORT OF A CASE

A white woman, 47 years of age, of Polish ancestry, presented an uneventful early history, free from any unusual diseases, dissipation or use of tobacco.

The onset of her disease was in November 1930. It consisted of a sharp pleuritic pain over the lower part of the chest on the right. There were fever, nightsweats, cough, expectoration, weakness and a loss of 38 pounds (17.2 Kg.) in weight.

On entry into the Municipal Tuberculosis Sanitarium she showed average development, a condition of feebleness, with a macular rash over both sides of the chest posteriorly. The mucous membranes and tongue were cyanotic; the teeth were in a good state of repair. The blood pressure was 106 systolic and 80 diastolic.

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14. Kretschmer, W.: Inaugural Dissert., Leipzig, 1904.
15. Pépère, A.: Centralbl. f. allg. Path. **15**:948, 1904.
16. Morelli, G.: Deutsche med. Wchnschr. **33**:805, 1907.
17. McCarthy, W. C.: Am. J. M. Sc. **151**:799, 1916.
18. Moise, T. S.: Arch. Int. Med. **28**:733, 1921.
19. Freid, B. M.: Medicine **10**:373, 1931.

The chest revealed cyanosis with a lag on the right. There was increased tactile fremitus on the right, and dulness on the upper two thirds of the right and upper half of the left side of the chest, anteriorly and posteriorly. There were râles, especially posteriorly, at the base of the right lung, with probably a large cavity in the upper lobe of the right lung. There were many râles on the left, but not so many as on the right. There was a marked dyspnea. The diagnosis was far advanced "B," questionably tuberculous. Three weeks before death the breathing on the right had become bronchial, and the left apex became hyperresonant.

The roentgenographic examination one month before death revealed a hazy right side with a left apex that was of normal density. The cardiac shadow was lost in an area of haziness that involved both midfields of the lungs and the base of the right lung.

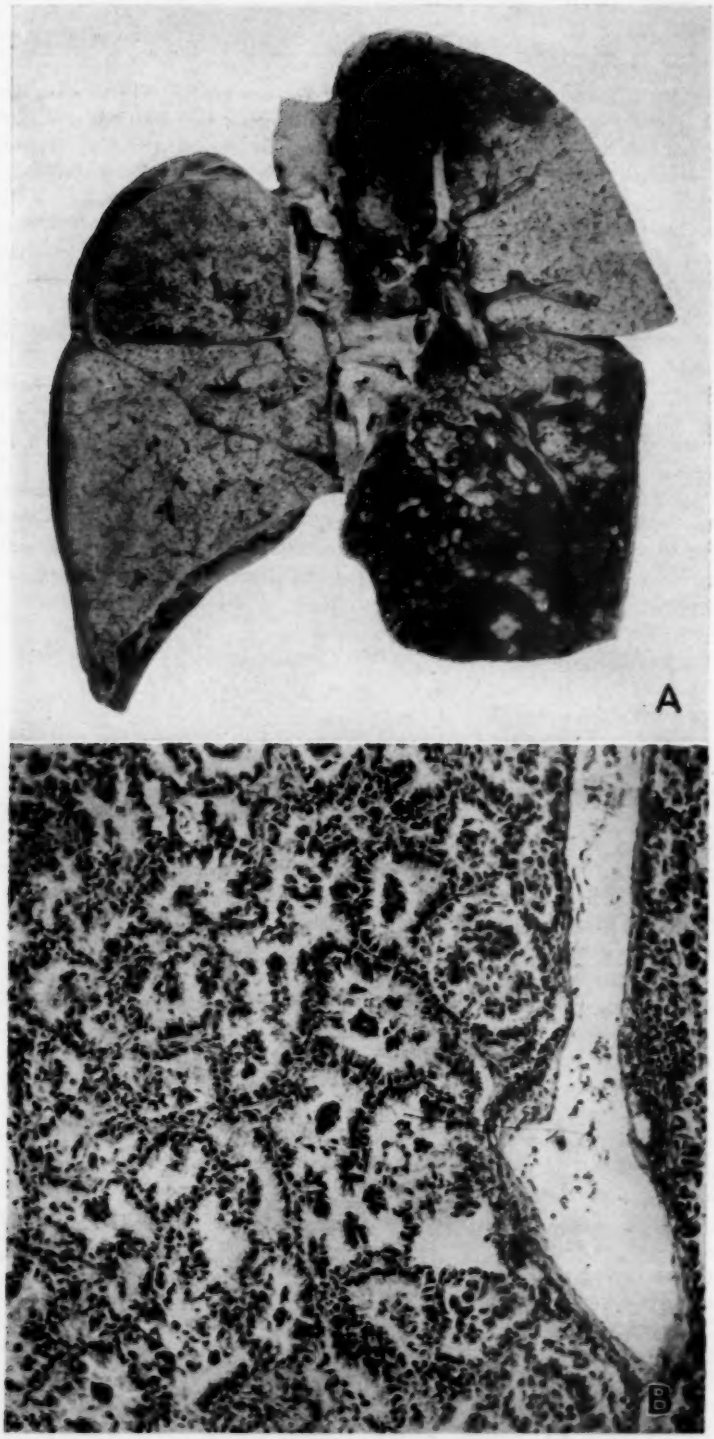
There was a four plus Kahn and Wassermann reaction, as well as a marked increase in neutrophilic polymorphonuclear leukocytes (31,200 leukocytes, 80 per cent of which were neutrophils), but everything else was practically normal. The pleural fluid revealed lymphocytes of varying sizes and a few monocytes of varying sizes but no mitotic figures. The cells were greatly disintegrated, and it may have been possible to overlook some malignant cells. No acid-fast or other micro-organisms were found. Actually many of the so-called monocytes were probably cancer cells.

The essential changes at autopsy were in the lungs, pleura and hilar lymph nodes.

The right lung consisted of a uniformly consolidated mass adherent throughout to the parietal wall by thin fibrous adhesions. It had the consistency of a uniform pneumonic consolidation. The surface made by a section from side to side through the midaxillary line was generally gray. The lower lobe was a uniform ashen gray, and the upper lobe more of an iron gray with small flecks of black pigment scattered throughout. This dark gray was confined principally to the middle and lower portion of the upper lobe, and gradually shaded off toward the periphery. The bronchi and blood vessels appeared normal. A section through the lung anteriorly and posteriorly to the midaxillary section revealed the same homogeneous, grayish consolidation involving every secondary lobule and alveolus. There was no normal lung tissue left in this lung.

The left lung was slightly different, in that the pleural spaces were obliterated by thinner adhesions; and the grayish consolidation was confined to a mass in the middle of the lung, measuring 15 cm. across. Toward the base and less toward the apex were many discrete isolated nodules varying in size from 2 to 10 mm., scattered out from the main mass.

Microscopically, there was a definite regularity of cell type and structure, and a regular sequence of changes depending on the age of the lesion from the oldest focus in the upper lobe of the right lung to the newest formation in the base of the left lung. A section from the base of the upper lobe of the right lung revealed heavy strands of fibrous tissue consisting of from four to six layers of connective tissue that appeared to have originated in the wall of the old alveolus. Some of these bands were fused together into heavy fibrous cords enclosing occasionally dark purple masses, some of which were from 30 to 50 microns in diameter and seemed to contain disintegrated nuclei undergoing calcification. In some of the open spaces could be seen disintegrating cells arranged singly, in pairs or in irregular rows. Most of these cells were angular with irregular nuclei and irregularly stained cytoplasm and nuclei. In some of the open spaces a few low columnar cells could be seen adherent to the walls. A section through the solid ashen gray



A, photograph showing a sagittal section through the lungs anterior to the bifurcation of the bronchi. *B*, low power photomicrograph of the uniform gray portion of the lower lobe of the right lung; × 95; hematoxylin and eosin stain.

portion revealed completely desquamated alveoli with a complete replacement of alveolar cells by low columnar epithelium. These cells appeared in many places like the low columnar cells of the bronchioles, but there was no mucus or cilia. Sometimes the nucleus was situated at the base, and sometimes at the free end of the cell. The nuclei varied slightly in size and staining. Some had a dense wall with exaggerated chromatin material, while others were pale-staining and larger, and contained larger nucleoli. Few, if any, mitotic figures could be seen. Some of these false alveoli were beginning to show a buckling of the new growth in the form of papillary projections into the lumen, and some of the papillary growth was detached. In the detached cells there was a definite tendency for them to become less columnar in form and to spread and resemble more cuboidal and basal cells of the epithelium. Occasionally, there appeared a rather large cell with a clear vesicular nucleus.

In the section taken through the uninvolved portion of the left lung it was possible to discern better the mechanism of the spread of the process. Here there was almost a complete desquamation of alveolar epithelium. A few alveolar cells still remained in the lumen in certain parts. There were scattering accumulations of foreign cells in the swollen bronchioles that showed signs of spreading out into the neighboring naked alveoli. No definite vascular emboli could be found, but there were many bronchial plugs. It was concluded that the metastases were taking place either by the lymphatics or by direct implantation. In many old alveoli could be found single cells or cells arranged in small adenomatous groups of four, six or more. As the nodules became larger they became adherent to the bare walls of the alveoli, and using them as a framework, they began to assume an alveolar arrangement. The only metastasis found was a 1 cm. nodule in a hilar lymph node. Many other lymph nodes were carefully sectioned, but contained no demonstrable metastasis. In this one metastasis the cells still maintained their alveolar arrangement around the lymph sinuses, but there was much fibrous replacement between these sinuses. No lymphoid tissue was present in the nodule. The picture was that of heavy fibrous cords outlining sinuses that were lined by a mixed type of cell, ranging between a cuboidal and a low columnar cell. The nuclear and cytologic appearances were much the same as those in the lung. There was one difference, and that was that the cells out in the lumen showed signs of acquiring a polyhedral form with here and there a very large vesiculated nucleus containing a large nucleolus. Occasionally there were twin cells, and very rarely could be seen what was interpreted as mitotic figures.

The other organs were negative so far as anything pertinent to this report was concerned.

SUMMARY

A report is made of cancer of the lung of a uniform low columnar cell type which spread directly from one alveolus to another until all of the right lung and the middle portion of the left lung were a consolidated mass of ashen gray appearance. The cells first supplanted the normal alveoli and maintained an alveolar arrangement. Later, they formed papillary growths into the alveoli. In the older region the cells became disintegrated. The origin seems probably to have been somewhere between the lower respiratory bronchioles and the alveoli. Inasmuch as there has never yet been any proof to show that cancers of the lung originate from pulmonary alveolar cells, it would seem that any suggestion of origin from this source must be held in abeyance at least until the precursor of the alveolar cell is established.

Clinical Notes

ISOLATION FROM HUMAN TISSUES OF EASILY VOLATILE ORGANIC LIQUIDS AND THEIR IDENTIFICATION

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A number of organic liquids of low boiling point are used in dry-cleaning, as general solvents, as fire-extinguishers, as anesthetics and as therapeutic agents in hookworm disease. Among these substances may be mentioned ethyl chloride, ethylene chloride, propylene dichloride, carbon tetrachloride, dichlor-difluormethane, chloroform, carbon bisulphide, benzene and diethyl ether. Fatalities from drinking some of these liquids or from inhaling their vapors have occurred and will occur from time to time. The menace to human life becomes apparent when the liquids are used in confined spaces and in nonventilated rooms. The layman, unwary of the toxicity of many of them, inhales the vapors with impunity until unconsciousness and death result.

The problem that confronts the toxicologist in cases of death due to poisoning with any of the aforementioned volatile liquids is to isolate them from the organs and establish their identity. The accepted technic for the isolation of volatile substances from tissues is steam distillation. The resulting distillate is a dilute solution of the volatile liquid in water. In cases of death from acute poisoning, if 500 Gm. of brain, liver or lung tissue is used for analysis there is an average of only about 0.3 cc. of the poisonous volatile organic liquid in 200 cc. of the aqueous distillate. The ordinary procedure for the identification of toxic substances in distillates from tissues is the application of color or precipitation reactions. With the dilute solutions of the volatile liquids just mentioned, no specific tests are available at the present time, and therefore there is no definite means of establishing the presence of a particular toxic substance with certainty.

The problem that we set out to solve was whether relatively small quantities of these organic liquids, if present in tissues, could be isolated in pure form. Were this possible, the identification of any one of the liquids could be accomplished by means of the determination of physical constants, such as the boiling point, the refractive index, the specific gravity and the molecular weight and also by micro-analysis for ultimate elementary composition.

Gettler and Siegel [1] described a method for isolating ether (diethyl ether) from human tissues. The experiments we wish to report here are a continuation of that study. Our set-up for the isolation of organic liquids of low boiling point (95 C. or lower) serves both for distillation and for rectification. The apparatus [2] is described in two parts (figs. 1

Contribution from the chemical laboratories of the Chief Medical Examiner's Office, Bellevue Hospital, and Washington Square College, New York University.

1. Gettler, A. O., and Siegel, H.: Arch. Path. **17**:510, 1934.

2. Made by Eck & Krebs, New York.

and 2). Dead spaces within the apparatus and corks or rubber stoppers have been entirely avoided, because experiments have proved that losses in the liquid to be isolated are caused by their presence.

ANALYTIC PROCEDURE

Apparatus for Steam Distillation (fig. 1).—The apparatus consists of: *a*, a distilling flask with a capacity of 2 liters; *b*, a bath for boiling water; *c*, a glass tube sealed into the side of the distilling flask for the delivery of the steam; *d*, an interchangeable no. 15 ground glass joint for connecting the distilling flask with the condenser; *e*, a water-cooled condenser; *f*, the bulb of the rectification flask, for the reception of the distillate from the tissues; *g*, an ice bath; *h*, a glass tube

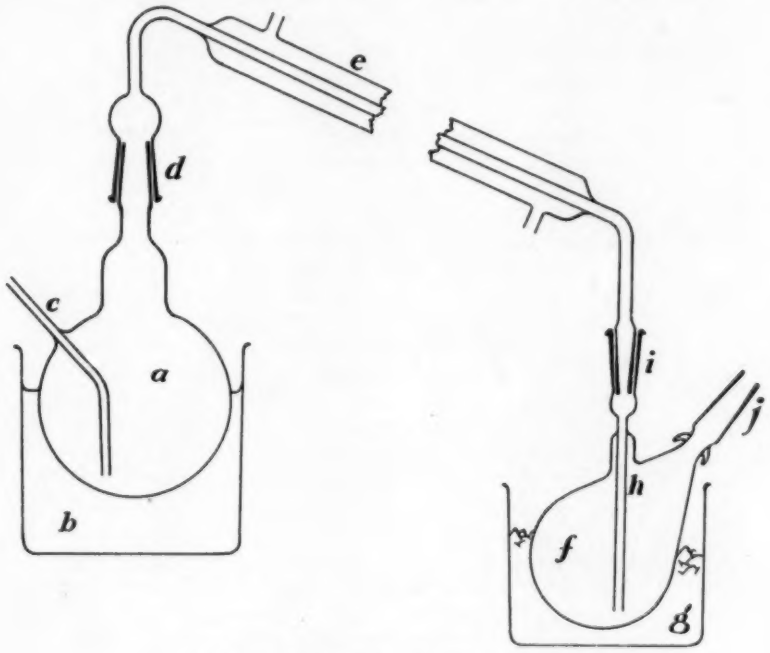

Fig. 1.—Apparatus for steam distillation.

sealed into the side of the rectification flask; *i*, an interchangable no. 7 ground glass joint for connecting the condenser with the bulb of the rectification flask which is used as a receiver for the distillate, and *j*, an interchangeable no. 9 ground glass joint used during rectification (fig. 2).

Method of Distillation of Volatile Organic Liquids from Tissues.—The tissues removed at autopsy are at once placed in glass jars, tightly sealed and put in a refrigerator. When ice-cold, about 600 Gm. is quickly ground up. The grinder is previously cooled by the application of ice. Five hundred grams of the ground material is rapidly weighed out, mixed with 200 cc. of ice-cold water and introduced into the 2 liter distilling flask (fig. 1*a*). An additional 300 cc. of water and 1 cc. of liquid petrolatum are added. The apparatus is then set up for steam distillation as indicated in figure 1. The steam distillation is continued until about 200 cc. of distillate has collected in the ice-cooled bulb of the rectification flask (fig. 1*f*). Experiments have shown that this amount is ample for the recovery

of practically all of the volatile organic liquid that may be present in the tissues. The rectification bulb and its contents are then removed from the distilling chain and kept cold by being surrounded with cracked ice. Two hundred and fifty grams of anhydrous calcium chloride is gradually added to the distillate in the flask while the solution is kept well mixed to prevent warming up. The purpose of the

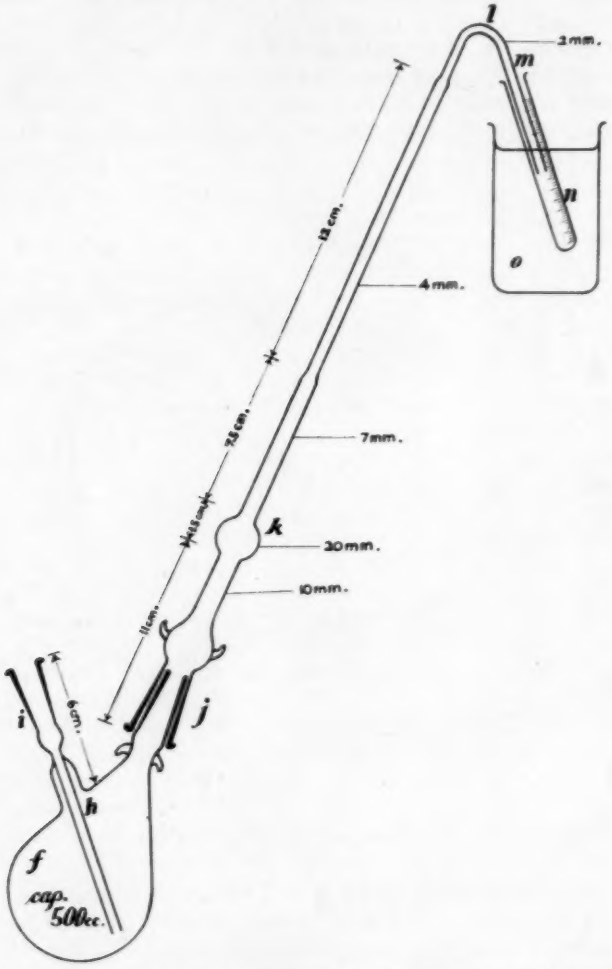

Fig. 2.—Rectification flask for isolation of volatile organic liquids.

addition of calcium chloride is to effect a salting out of the volatile liquid present and also to lower the vapor pressure of the water. About 1 Gm. of granulated zinc is then added to prevent bumping. The rectification bulb and its contents are then set up for rectification as indicated in figure 2.

Rectification Flask for Isolation of Volatile Organic Liquids (*fig. 2*).—The apparatus consists of: *f*, a distillation bulb (capacity, 500 cc.); *h*, a glass tube fused into the side of the distillation bulb which acts as a safety-valve; *j*, an interchangeable no. 9 ground glass joint; *k-l*, a reflux condenser (air-cooled); *m*,

a microcondenser (cooled by a freezing bath); *n*, a tube for collection of the distillate, the inside diameter of which measures 6 mm. and which is graduated in twentieths of a cubic centimeter, and *o*, a solid carbon dioxide-acetone cooling bath.

The rectification flask used in these determinations is slightly modified from that used by Gettler and Siegel.[1] It is constructed in two parts, *f* and *k l m*, connected by a ground glass joint (*j*). This change in structure facilitates the introduction and removal of material into and from the flask.

Method for Isolation of Volatile Organic Liquids from Tissue Distillates: Rectification.—In order to obtain the best results it is essential that the condenser parts *k*, *l* and *m* of the rectification flask be perfectly clean. This is best accomplished by treating them with hot concentrated nitric acid, or by letting them stand overnight in a cleaning mixture of sulphuric and chromic acid. Before attaching the condenser to the bulb of the rectification flask, the inner surface of the portion of *k*, *l* and *m* should be thoroughly dried by playing a gentle flame over the outer surface. The receiving tube (*n*) is kept in a cooling bath (*o*). With volatile liquids of extremely low freezing points, the cooling bath consists of carbon dioxide snow in acetone. For the liquids which freeze at a point only a little below 0 C. an ice and salt mixture is used. For benzene which freezes at 5.4 C. ice-water is satisfactory. To start the rectification the material in the bulb of the flask is heated carefully and slowly, an asbestos-centered wire gauze and a micro-burner being used. As soon as the liquid in the bulb begins to boil, the flame is regulated so that the liquid boils gently for about fifteen minutes. During this time, the steam (as indicated by a visible rise of the condensate or by running the hand along the tube of the flask and determining the height of the steam by the temperature of the tube) must not be permitted to rise beyond *k*. This is done by properly regulating the flame. The part of the tube from *k* to *l* acts as a reflux for the steam, whereas the vapors of the volatile liquid which rise past *l* condense and collect in the receiver *n*. After gentle boiling has been continued for fifteen minutes, the flame is gradually increased so that the steam is made to rise slowly (in one to two minutes) until it just passes the bend of the tube (*l*). From this point the procedure varies according to the cooling bath used. If a carbon dioxide snow-acetone mixture is used, the distillation is continued at the same constant rate. After the volatile organic liquid has distilled over, steam will follow. Beyond *l* the steam will condense and freeze. Ice will clog the tube (*m*). The pressure produced within the flask will force the liquid in the bulb out through the safety-tube (*h*). This occurrence indicates the end-point in the distillation. If an ice and salt or a plain ice-water cooling bath is used, the water vapor rising into *m* may not freeze and clog the tube, and hence no back pressure will be produced. In this case the end-point of the distillation is signified when the bend (*l*) attains the temperature of boiling water. Rectification is now completed. The volatile liquid, if present, will be found in the calibrated receiver (*n*).

The receiving tube is now removed from the cooling bath, lightly stoppered and allowed to stand at room temperature until the ice present has melted. The tube and contents are at once centrifugated for two minutes and then placed in ice-cold water for five minutes. The volume of the layer of isolated liquid is then read.

Identification of the Isolated Liquid.—In order to identify the isolated liquid, the following tests may be applied: (*a*) microdetermination of the boiling point by the method of Emich,[3] also described by Gettler, Niederl and Benedetti-

3. Emich, F.: Monatschr. f. Chem. **38**:219, 1917.

Pichler;[4] (*b*) microdetermination of the molecular weight;[5] (*c*) micro-analytic determination of carbon and hydrogen,[6] and (d) microdetermination of halogen.[7]

In the present study we have made use of the microdetermination of the boiling point [5] for the identification of the isolated liquid. Experiments have convinced us that the isolated volatile liquid need not be dried for use in the determination of the boiling point.

The volatile liquids which we succeeded in isolating from tissues are ethyl chloride, ethylene chloride, propylene dichloride, carbon tetrachloride, dichlor-difluormethane, chloroform, carbon bisulphide, benzene and diethyl ether. Identification of the particular liquid present was accomplished by microdeterminations of the boiling point. One set of values obtained in our experimental study is charted in the table.

Recovery and Boiling Point of Isolated Volatile Organic Liquids

Volatile Liquid	Boiling Point of the Liquid, Degrees, C.	Amount of Liquid Added to 200 Cc. of Water, Cc.	Amount of Liquid Added to 500 Gm. of Tissue, Cc.	Amount of Liquid Recovered, Cc.	Boiling Point of the Isolated Liquid, Degrees, C.
Ethyl chloride	12.2	0.3	...	0.08	12.2
	12.2	...	0.3	0.05	12.4
Ethylene chloride	83.2	0.3	...	0.27	83.3
	83.2	...	0.3	0.22	83.1
Propylene dichloride	95.6	0.3	...	0.27	95.7
	95.6	...	0.3	0.19	95.7
Carbon tetrachloride	76.7	0.3	...	0.27	76.1
	76.7	...	0.3	0.05	68.0*
	76.7	...	1.0	0.10	74.0
Dichlor-difluormethane	39.4	0.3	...	0.26	39.4
	39.4	...	0.3	0.17	40.0
Chloroform	62.1	0.3	...	0.21	62.1
	62.1	...	0.3	0.09	62.2
Carbon bisulphide	46.1	0.3	...	0.27	46.0
	46.1	...	0.3	0.09	46.0
Benzene	80.5	0.3	...	0.25	80.1
	80.5	...	0.3	0.10	80.2
Diethyl ether	34.8	0.3	...	0.25	34.9
	34.8	...	0.3	0.24	34.7

* Carbon tetrachloride isolated from tissues always gave an abnormally low boiling point, which we have proved to be due to the fact that some of the tetrachloride is converted into chloroform, the mixture of chloroform and carbon tetrachloride giving the abnormally low boiling point. By means of Emich's microfractionating tube [4] the chloroform and the carbon tetrachloride can be separated. If this procedure is carried out, the fraction containing the tetrachloride gives the correct boiling point.

SUMMARY

The method that is described for isolating organic liquids of low boiling point from tissues makes use of a specially constructed distillation apparatus and a newly devised microrectification flask which are described in detail. The isolated volatile liquids are identified by means of microdetermination of the boiling point. The following volatile liquids have been isolated from tissues and identified: ethyl chloride, Ethylene chloride, propylene dichloride, carbon tetrachloride, dichlor-difluormethane, chloroform, carbon bisulphide, benzene and diethyl ether.

4. Gettler, A. O.; Niederl, J. B., and Benedetti-Pichler: Mikrochemie **11:** 178, 1932.

5. Niederl, J. B.: Ztschr. f. anal. Chem. **77:**169, 1929.

6. Niederl, J. B., and Roth, R. T.: Indust. & Engin. Chem. **6:**272, 1934.

7. Elek, A., and Hill, D. W.: J. Am. Chem. Soc. **55:**2552, 1933.

General Review

THE NONSUPPURATIVE FORMS OF ENCEPHALITIS

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MINNEAPOLIS

Cases of nonsuppurative inflammation of the central nervous system include all cases of encephalitis except those characterized by a polymorphonuclear cell exudate. The clinical types of nonsuppurative encephalitis are numerous. The condition occurs chiefly as the result of infection or intoxication. Infection is the most frequent source. The nervous involvement may be either primary or secondary. The former includes conditions such as epidemic encephalitis, the type of encephalitis observed in the St. Louis epidemic, hemorrhagic encephalitis and herpetic encephalitis. The latter includes cerebral involvement secondary to infectious diseases, which is by no means rare, and to certain intoxications. There is probably no infectious disease that has not been reported as complicated by some involvement of the central nervous system.

There are many excellent studies of the clinical picture in the various forms of encephalitis, but reports of the pathologic lesions, although numerous, are widely scattered through the literature and merit a concise review. An attempt will be made to present a brief account of the principal findings that have been reported. I have studied several cases of encephalitis, and reports of these will also be incorporated in this study.

PRIMARY NONSUPPURATIVE ENCEPHALITIS

Epidemic Encephalitis.—Von Economo [1] first gave a detailed clinical and pathologic picture of this acute inflammation of the gray substance of the nervous system.

Grossly the changes are slight. The brain appears rather soft and hyperemic. On section a punctiform prominence of the blood vessels occasionally appears, but there are no hemorrhages. Macroscopic hemorrhages in the brain are rare, but they have been reported.

The microscopic picture is characteristic. Infiltration by perivascular mononuclears is the salient feature. Isolated hyperemic vessels in the

From the Department of Pathology, University of Minnesota.

1. von Economo, C.: Encephalitis Lethargica: Its Sequelae and Treatment, New York, Oxford University Press, 1931, p. 26.

gray matter show a dense accumulation of lymphocytes in the adventitial sheaths. The extensive infiltration surrounds in a cufflike manner the walls of the vessels, which appear unchanged. The involved vessels are mostly medium-sized veins. Besides the lymphocytes, young plasma cells and a few polymorphonuclears are often present among the infiltrating cells.

Occasional small perivascular hemorrhages occur in restricted areas. These are slight and are often entirely absent, even in severe cases, so that they cannot be considered as characteristic of the disease.

The changes in the nerve parenchyma consist mainly in small isolated foci of infiltrate which show no tendency to softening. There is complete absence of fat granule cells. Many accumulations of glia cells are seen in the vicinity of the larger ganglion cells, where they form the "glia-lawns." They may also occur independently of the ganglion cells and vessels in small round, rosette-shaped masses.

There is destruction of nerve cells in the substantia nigra, the thalamus, the basal nuclei, the cortex and the spinal cord. One often sees isolated ganglion cells with varying degrees of degeneration, from slight tigrolysis to swelling and hyalinization of the protoplasm, shifting of the nucleus to the periphery, pallor and disappearance of the nucleus and, finally, the formation of "ghost cells." Although any part of the central nervous system may be attacked, from the cortex to the sacral cord, the brain stem is chiefly affected.

St. Louis Epidemic Type of Encephalitis.—During the summer of 1933, an outbreak of encephalitis occurred in St. Louis, involving 1,065 persons, with 197 deaths. Clinically, this epidemic differed from the 1918 outbreak described by von Economo: It occurred during the hot months; oculomotor paralysis was absent, and in the patients who survived recovery was rapid and without encephalitic sequelae. In these features this outbreak bears a marked similarity to the encephalitis of the Japanese epidemics of 1924 and 1927.

The lesions in the central nervous system in the St. Louis epidemic have been described by Weil [2] and McCordock, Collier and Gray.[3] They consisted of disseminated encephalitis and myelitis involving both the gray and the white matter and accompanied by mild leptomeningitis, which was most marked at the base of the brain. The exudate consisted chiefly of lymphocytes, plasma cells and histiocytes. Polymorphonuclears were absent. The encephalitic lesions consisted in perivascular infiltration by round cells and in the formation of isolated foci of proliferated glia. The perivascular exudate involved both the veins and the

2. Weil, A.: Arch. Neurol. & Psychiat. **31**:1139, 1934.

3. McCordock, H. A.; Collier, W., and Gray, S. H.: J. A. M. A. **103**:822, 1934.

arteries of the gray and white substance and was formed chiefly of small lymphocytes. The foci of glial proliferation were irregularly disseminated through the brain, independently of the vessels. They were composed primarily of oligodendroglia. Perivascular hemorrhages were absent. Some nerve cell degeneration was observed in most cases.

Histologically, these lesions resembled somewhat those described by von Economo in 1918. However, Webster and Fite [4] showed that there is no cross-neutralization of the serum of the epidemic encephalitis of 1918 with that of the encephalitis of the Japanese epidemic and that of the encephalitis of the St. Louis epidemic. They believe that each type was caused by a different virus.

Hemorrhagic Encephalitis.—The first cases of hemorrhagic encephalitis were described by Wernicke.[5] He reported 3 cases, in all of which the condition terminated fatally and autopsy showed numerous petechial hemorrhages in the brain substance. Strümpell [6] reported 2 cases in which the condition clinically resembled encephalitis and in which autopsy showed markedly distended capillaries, hemorrhages in the white matter and some glial proliferation. In neither case were the ganglion cells involved. Strümpell considered his cases examples of primary acute hemorrhagic nonsuppurative encephalitis, a term that aptly describes the malady. Stäussler [7] also reported 2 cases of hemorrhagic encephalitis. His description of the cases (the acute onset in previously healthy persons and the pathologic picture of numerous small petechiae throughout the brain) fits nicely the condition of hemorrhagic encephalitis. More recently, Bell [8] referred to this malady and described accurately the lesions in the brain, of which I [9] have published a complete account. The disease is characterized as an acute ailment in previously healthy young persons, with a sudden onset, headache, an abrupt rise in temperature and rapid loss of consciousness. Convulsions are common; the extremities are spastic, and the reflexes are frequently abnormal and variable. Death ensues within from a few hours to several days after the onset.

The postmortem observations are limited to the brain, which reveals a uniform and striking picture. The lesions are chiefly hemorrhagic and are situated mainly in the white matter. The hemorrhages vary widely in number and size, from extensive extravasations which destroy much

4. Webster, L. T., and Fite, G. L.: Science **78**:463, 1933.

5. Wernicke, cited by Jacobäus, H.: Deutsche Ztschr. f. Nervenh. **5**:334, 1894.

6. Strümpell, A.: Deutsches Arch. f. klin. Med. **47**:53, 1891.

7. Stäussler, E.: Wien. klin. Wchnschr. **15**:61, 1902.

8. Bell, E. T.: A Text-Book of Pathology, Philadelphia, Lea & Febiger, 1930, p. 549.

9. Baker, A. B.: Am. J. Path., to be published.

brain tissue to tiny perivascular bleedings (fig. 1). In the brains of patients who survive the first few days there are often areas of nonhemorrhagic perivascular demyelinization which are invaded by scavenger cells. Consistent specific changes in the ganglion cells have not been observed. An occasional blood vessel shows a slight perivascular infiltration by mononuclears. A few widely scattered polymorphonuclears can be detected in the areas of degeneration.

Brain tissue from a patient with hemorrhagic encephalitis has proved virulent to rabbits on intracerebral inoculation. It has been possible to transmit the infectious agent through a series of rabbits without an appreciable decrease in its strength of action.

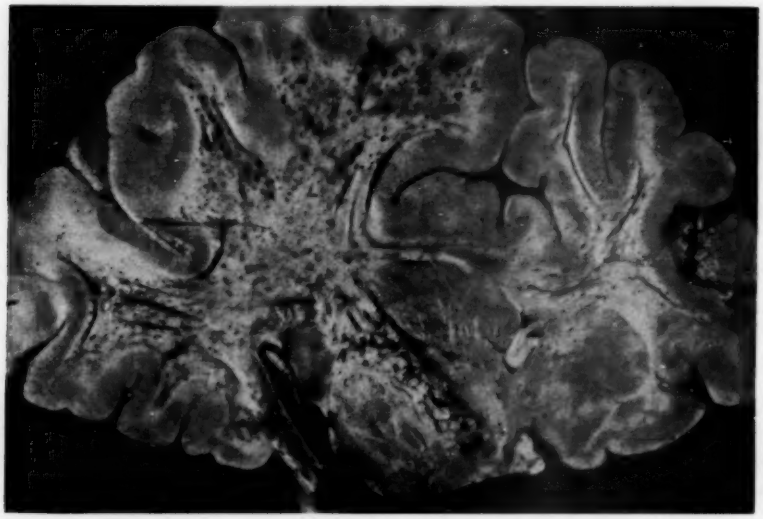


Fig. 1.—Photograph of a section through the brain of a 30 year old woman who died of hemorrhagic encephalitis. The hemorrhages are sharply localized to the white substance.

Herpetic Encephalitis.—From a pathologic standpoint, herpetic encephalitis is unimportant, since death is infrequent. Since the herpes virus is, however, commonly used in experimental work, it is necessary to consider it briefly.

The commonest situation of the primary eruption of herpes simplex is the lips, cheeks, nose, ears, or mucous membrane of the mouth. These lesions are usually associated with a cold, meningitis, pneumonia, scarlet fever, paratyphoid fever or some other disease. Scheer [10] described a case of transfer of herpes from one child to another by a bite. The most important work in this field, however, has been experimental.

10. Scheer, K.: München. med. Wchnschr. **78**:613, 1931.

Grüter,[11] in 1912, transferred the herpetic lesion from one animal to another by material from a herpetic vesicle. The work acted as the stimulus for more extensive work chiefly by Da Fano,[12] Lipschütz,[13] Goodpasture,[14] Flexner [15] and Cowdry.[16] Da Fano, in 1923, described the encephalitic lesions of herpes as present throughout the central nervous system, chiefly in the hemispheres. The lesions consisted in widespread infiltration by small cells, intense nerve cell degeneration and diffuse proliferative phenomena on the part of some of the fixed cells. Lipschütz, in 1921, described the characteristic inclusions within the nuclei of the cells in the herpetic lesions. This observation was verified by Cowdry [16] and Goodpasture.[17]

Spooner,[18] in 1930, again summarized the histologic changes of the brain in herpes. In his studies the meninges showed a slight infiltration by mononuclear cells but not by polymorphonuclears. The dilated blood vessels were surrounded by perivascular cuffs of mononuclears. The nerve cells showed nuclear swelling, chromatolysis, neuronophagia, satellitosis and nuclear inclusions. He could not observe perivascular or free hemorrhages or demyelinization of nerve fibers.

Flexner [19] observed lesions chiefly in the forebrain, midbrain and medulla. The spinal cord was much less involved. Goodpasture [20] produced contact encephalitis in rabbits and observed that most of the lesions were in the medulla about the central terminations of the sensory divisions of the fifth and ninth nerves. He assumed that these lesions occur whenever the disease is contracted through the mucous membranes of the mouth, nose or throat.

Since most of these lesions were experimental, one can only speculate as to what the lesions in man may be.

ENCEPHALITIS SECONDARY TO INFECTIOUS DISEASES

Encephalitis Following Measles.—The first reports on the nervous complications in measles were by Odier, in 1722; Nevel, in 1724, and Lucus, in 1790. Since that time a great number of cases have been reported. These present a diversity of clinical symptoms but possess

11. Grüter, W.: Arch. f. Augenh. **70**:241, 1912; München. med. Wchnschr. **71**:1058, 1924.
12. Da Fano, C.: J. Path. & Bact. **30**:67, 1927; **26**:85, 1923.
13. Lipschütz, B.: Arch. f. Dermat. u. Syph. **136**:428, 1921.
14. Goodpasture, E. W.: Am. J. Path. **3**:395, 1927.
15. Flexner, S.: J. Gen. Physiol. **8**:713, 1927.
16. Cowdry, E. V.: Arch. Path. **10**:23, 1930.
17. Goodpasture, E. W.: Am. J. Path. **1**:1, 1925.
18. Spooner, E. T. C.: Am. J. Path. **6**:767, 1930.
19. Flexner, S.: J. Exper. Med. **41**:215, 1925.
20. Goodpasture, E. W.: Am. J. Path. **1**:29, 1925.

a fairly constant pathologic picture (Sotow,[21] Fairbanks,[22] Marsh,[23] Lowenburg and Schaller,[24] McLendon [25] and Benn [26]).

Nervous complications in infectious diseases are, in general, rather infrequent. Beach,[27] in a series of 2,000 cases, found such involvement in but 37, or 2 per cent; in 11 of these the involvement occurred in measles, in 9 in scarlet fever, in 8 in whooping cough, in 6 in typhoid, in 1 in smallpox, and in 1 in diphtheria. Boenheim [28] observed 5,940 cases of measles with nervous complications in but 0.4 per cent.

The symptomatology in encephalitis following measles is variable, depending on the location of the lesions. Ford [29] and Jenkins,[30] in reviewthe literature, described the following course of involvement in a typical case: The onset is usually from four to six days after the appearance of the eruption and is characterized by drowsiness and a secondary rise in temperature. There may be headache, vomiting and dilatation and fixation of the pupils, with congestion or edema of the optic nerve heads. The extremities may be flaccid or spastic and the reflexes variable. The drowsiness gradually becomes more profound until the patient is comatose. In most cases the somnolent state passes off after a few hours or a few days, and the child passes through a state of irritability which may manifest itself in choreiform movements, spastic weakness of the extremities, aphasia and ataxia or merely in a complete change of personality to a state of naughtiness and bad temper. In the latter condition unmotivated screaming, irritability, excitement and abusive language are common. Recovery is usually slow, and about 65 per cent of the patients show some residual symptoms; 17 per cent remain mentally defective. Some patients show only hemiplagia and aphasia. Gilman [31] reported a case in which there was complete recovery and in which only the auditory and visual centers were involved. Some patients may show a cerebellar type of ataxia, with loss of muscle tone, loss of equilibrium and scanning speech. Others may show only injury of the cord, with little or no other involvement.

Many complete reports of autopsies have been published. In a typical case the dura is tense but the convolutions of the brain are normal.

21. Sotow, A. D.: Jahrb. f. Kinderh. **50**:1, 1899.
22. Fairbanks, A. W.: Arch. Pediat. **24**:770, 1907.
23. Marsh, N. P.: Brit. J. Child. Dis. **7**:241, 1910.
24. Lowenburg, H., and Schaller, A. L.: Arch. Pediat. **43**:73, 1926.
25. McLendon, P. A.: Arch. Pediat. **43**:544, 1926
26. Benn, E. C.: Brit. J. Child. Dis. **28**:22, 1931.
27. Beach, F.: Brit. M. J. **2**:707, 1895.
28. Boenheim, C.: Ergebn. d. inn. Med. u. Kinderh. **28**:620, 1925.
29. Ford, F. R.: Bull. Johns Hopkins Hosp. **43**:140, 1928.
30. Jenkins, P. K.: J. Missouri M. A. **27**:65, 1930.
31. Gilman, W. R.: Boston M. & S. J. **149**:177, 1903.

On section of the brain one can see many foci of softening in the white substance. The lesions are primarily in the white matter of the cerebrum, pons and cerebellum. They appear as yellowish-red, soft, opaque spots, which are regularly outlined. Microscopically the lesions are the same everywhere. The center of each lesion consists of a dilated thin-walled vessel surrounded by an almost circular area of rarefied brain tissue. All the areas of perivascular demyelinization are invaded by numerous fat granule cells. Around the central vessel, the fat-containing cells are arranged as a mantle. The axis-cylinders appear intact. Ford quoted Brock, who claimed that these lesions do not contain hemorrhages or inflammatory cells such as lymphocytes, leukocytes or plasma cells. Musser and Hauser [32] studied the lesions of the brain in 8 cases; in these, areas of perivascular hemorrhage were common. They observed also occasional areas of lymphocytic infiltration. Greenfield [33] reported cuffs of mononuclears about many of the veins in the focal lesions, but he did not specify the origin of these cells. In his cases hemorrhages were inconspicuous. Mässe reported several unusual cases in which there were involvement of the axis-cylinders and an overgrowth of neuroglia. Wohlwill [34] described degeneration of the nerve tissue of the cord with glial reaction. In one of his cases involvement of the ganglion cells occurred.

Recently, Moore and McCordock [35] described encephalomyelitis in an 8 year old child, which developed one week after the onset of measles. At autopsy perivascular demyelinization was the most conspicuous lesion within both the brain and the spinal cord. Perivascular cuffing with mononuclear cells occurred around only a few of the veins. Congestion and small hemorrhages about the blood vessels were also present.

The whole process is characterized by focal destruction of myelin, with relatively good preservation of the axis-cylinders, collections of lipoid in the fat granule cells and beginning gliosis at the margin of the foci of injury. The veins in the white matter of the brain are chiefly involved. They are definitely distended.

I studied 2 cases of encephalitis following measles. One was that of a child 2½ years old, the other that of a child of 4 years. In both the onset was typical, and death resulted after a few days. Spinal tap on the older of the two children a few hours before death showed 586 cells per cubic millimeter. Cultures of brain tissue and of the spinal fluid were negative. At autopsy the external surface of the brain was injected; there was an increase in subarachnoid fluid, but no other changes were present. Microscopic study failed to reveal the change so frequent

32. Musser, J. H., and Hauser, G. H.: J. A. M. A. **90**:1267, 1928.

33. Greenfield, J. G.: Brain **52**:171, 1929.

34. Wohlwill, F.: Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

35. Moore, E., and McCordock, H. A.: Arch. Neurol. & Psychiat. **32**:560, 1934.

in encephalitis following measles, namely, perivascular demyelinization. Instead, many of the blood vessels were surrounded by densely packed masses of lymphocytes and plasma cells. These infiltrations were strictly localized to the immediate vicinity of the vessels, sometimes masking the structure of their walls but never extending outward into the surrounding tissue. An occasional polymorphonuclear could be detected among the other cells. No softening was observed about the vessels. A single small vessel with perivascular erythrocytes was seen.

When one compares the lesions found in these cases with those reported in the literature, one appreciates that as yet no specific pathologic picture can be described as diagnostic of the cerebral lesions following measles.

Encephalitis Following Whooping Cough.—Although there are numerous clinical reports of this condition, the pathologic study has been largely neglected. The reported cases show marked diversity. Mikulowski [36] reported edema and hyperemia of the brain. Boenheim [28] studied one patient who showed a gelatinous appearance of the meninges and a few punctate hemorrhages post mortem. The most complete study of encephalitis following whooping cough was made by Husler and Spatz,[37] in 1924. Grossly, the brains in their cases presented slight hyperemia and dilatation of the blood vessels. Microscopic examination revealed the most striking lesions in the nerve cells of the cortex. These consisted in loss of the staining properties of the cells, with obliteration of the normal Nissl picture. The nuclei remained normal. The alterations were most marked in the hippocampus major, where the cells were completely degenerated. Slight perivascular lymphocytic infiltration was observed in the white substance, as well as mild cellular infiltration in the pia-arachnoid. No focal lesions were detected.

Askin and Zimmerman [38] could not observe any changes in the ganglion cells, any petechiae in the cortex or meninges or any evidence of meningitis. They described the lesions in their cases as scattered focal collections of small mononuclear cells. The largest collections lay at varying distances from the ependyma lining the inferior horns of the lateral ventricles, although smaller collections were present in each corpus striatum. There was no true perivascular collection of mononuclears.

Encephalitis Following Smallpox.—This condition is rare. Marsden and Hurst [39] reported 9 cases in a series of 40,254 patients with smallpox. The nervous symptoms may occur at any stage of the disease,

36. Mikulowski, V.: Rev. franç. de pédiat. **4**:646, 1928; Jahrb. f. Kinderh. **124**:103, 1929.

37. Husler, J., and Spatz, H.: Ztschr. f. Kinderh. **38**:428, 1924.

38. Askin, J. A., and Zimmerman, H. M.: Am. J. Dis. Child. **38**:96, 1929.

39. Marsden, J. P., and Hurst, E. W.: Brain **55**:181, 1932.

even during the incubation period or advanced convalescence (Spiller [40]), but the most frequent time of onset is from five to thirteen days after the appearance of the rash.

Clinically, the neurologic findings in these patients are divided into two main groups (Aldrich,[41] Spiller,[40] Bernhardt,[42] Marsden and Hurst,[39] and Troup and Hurst [43]). In the first group the most prominent feature is a disturbance of speech. Improvement is slow, but the course is favorable. The lesions of this type are obscure. The second group is characterized by paralysis of the limbs, with or without sphincteric disturbances. Sensation is usually not disturbed. Sometimes the paralysis is rapid and ascending. Many cases prove fatal, and the patients who recover have residual symptoms, such as spastic weakness, muscle deformity and abnormal behavior.

The lesions in the nervous system following smallpox are primarily in the spinal cord (Spiller,[40] Aldrich,[41] Marsden and Hurst [39] and Troup and Hurst [43]), although Marsden and Hurst reported some alterations in the cerebrum. Grossly, the brain showed grayish translucent rings throughout the white matter. Microscopically, there was demyelinization about numerous small vessels. Marsden and Hurst suggested that this lesion be called "acute perivascular myeliniclysis."

The chief lesions in the cord consist in intense perivascular demyelinization involving almost all the blood vessels. The areas often become so large that they fuse. Within the demyelinated areas there are numerous microglia in the various stages of metamorphosis, which are filled with globules of fat. Many vessels are surrounded by mononuclear cells, chiefly lymphocytes and plasma cells. The infiltration is rarely severe enough to form a complete collar about the vessel. The axis-cylinders within the demyelinated areas are somewhat damaged and in many cases entirely absent. Bernhardt [42] in one case could not observe any lesion microscopically in the entire central nervous system to account for the clinical symptoms.

Encephalitis Following Mumps.—Cerebral involvement in parotitis is rare. Although the literature contains numerous clinical reports of encephalitis following mumps, most of the patients recovered, and pathologic data are wanting. Most authors quote Larkin's [44] description of the cerebral lesions. The pia-arachnoid was congested. There were scattered areas of exudate, which followed the course of the blood vessels. The ventricles were distended with clear fluid. Microscopically,

40. Spiller, W. G.: Brain **26**:424, 1903.
41. Aldrich, C. J.: Am. J. M. Sc. **127**:198, 1904.
42. Bernhardt: Klin. Wchnschr. **8**:561, 1871.
43. Troup, A., and Hurst, W.: Lancet **1**:566, 1930.
44. Larkin, W. R.: Mil. Surgeon **44**:92, 1919.

the pia-arachnoid was infiltrated by large mononuclear cells, many of which extended into the cerebral cortex. Gordon [45] was able to kill monkeys by intracerebral inoculation with cultures of material from the throats of patients with mumps. The brains and spinal cords of the animals showed moderate lymphocytic infiltration of the pia-arachnoid and the cerebral cortex. Occasional nerve cells of the cortex and of the anterior horns of the cord showed degeneration. In no case were hemorrhages seen.

Because of the infrequency of such studies, a detailed description of a case of encephalitis following mumps seems warranted:

A girl, 4 years old, showed signs of bilateral parotitis five days before admission to the hospital. She did not, however, seem ill and continued to play about as usual. Two days after the onset of the illness she suddenly began to vomit, complained of headache and seemed feverish and drowsy. The drowsiness persisted and became more profound. On the day of admission she showed difficulty in breathing and threw her hands upward and doubled up as though in pain. She did not, however complain of pain. Her face was flushed, and the pupils were dilated. There was a peculiar distant stare in the eyes. The heart and lungs seemed normal. There were a slight rigidity of the neck and a positive Kernig sign. The Babinski sign was positive, but the patellar reflexes were normal. The spinal fluid was under normal pressure, was cloudy and contained 380 cells per cubic millimeter. The leukocyte count of the blood was 14,300. The temperature was 102.8 F. on admission and continued to rise. The patient died twelve hours after admission.

At autopsy all the internal organs were normal, both grossly and microscopically. The brain and meninges also appeared normal on gross examination. However, microscopic inspection confirmed the observations of the other investigators, especially of Larkin. Scattered throughout the pia-arachnoid was a mononuclear infiltration of moderate intensity. The large mononuclears tended to localize about the blood vessels and accompanied them into the brain tissue. No other cellular invasions were detected within the cerebrum. The white substance of the brain was unaltered, and the nerve cells were normal.

Encephalitis Following Chickenpox.—Many clinical reports of this type of encephalitis have been published by Wilson and Ford,[46] Brain,[47] Graham,[48] Tramer [49] and others, but in the literature only two complete autopsy studies have been recorded—one by Zimmerman and Yannet [50] and the other by Van Bogaert.[51] A discussion of the lesions in this type of cerebral involvement must, therefore, be based on the work

45. Gordon, M. H.: Lancet **1**:652, 1927.

46. Wilson, R. E., and Ford, F. R.: Bull. Johns Hopkins Hosp. **40**:337, 1927.

47. Brain, W. R.: Brit. M. J. **1**:81, 1931.

48. Graham, S.: Arch. Dis. Childhood **5**:146, 1930.

49. Tramer, E.: Med. Klin. **26**:1598, 1930.

50. Zimmerman, H. M., and Yannet, H.: Arch. Neurol. & Psychiat. **26**:322, 1931.

51. Van Bogaert, L.: Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:201, 1932.

of these authors. Grossly, the brain appears normal. Microscopically, the lesions consist in injury to the ganglion cells of the cortex and in perivascular demyelinization of the white substance. Zimmerman and Yannet's patient showed extensive swelling and vacuolation of all the nerve cells, while Van Bogaert's patient showed much less marked involvement. Both authors described large areas of perivascular demyelinization scattered throughout the white substance of the parietal, frontal and occipital lobes. Within these destroyed areas were numerous fat granule cells. Van Bogaert mentioned also destruction of the axis-cylinders in his case. No demyelinization was noted around the lateral ventricles, the aqueduct or the floor of the fourth ventricle. Zimmerman and Yannet reported small hemorrhages around some of the vessels, while Van Bogaert noticed only occasional perivascular infiltrations by mononuclear cells.

There appears to be such variation in these two cases that the question of a specific neuropathologic picture in this condition must await further reports. I studied a case of encephalitis in chickenpox, the report of which follows:

A 6 year old boy was taken ill twenty-two days previous to admission to the hospital. At that time a papular rash developed on his arms, hands and legs. The rash became vesicular, and after five days it began to dry up. However, two or three days later a new crop of lesions developed. About twelve days after the onset the illness became more severe. The patient cried out at intervals and stiffened out in bed. Seven days prior to admission he lost the ability to talk, although he seemed to understand what was said to him. The past history was insignificant.

Large vesicles were found about the margin of the hair line. The pupils were regular and reacted normally. There was no evidence of disease in the nose or throat. Slight cervical adenopathy was present. Fading discrete lesions were evident on the trunk and more recent cutaneous lesions on the arms and legs and on both the dorsal and the plantar surfaces of the feet. The child had a fixed expression; the eyes were staring. Either he would not or he could not talk. The head could easily be flexed on the chest, but the neck was somewhat stiff. The Kernig sign was negative. The abdominal and cremasteric reflexes were present; the patellar reflexes were hyperactive; ankle clonus and knee clonus were absent, and the Babinski sign was positive bilaterally. The child was able to make voluntary motions without assistance. The temperature was 98.4 F. and the pulse rate 132.

The spinal fluid was normal, and cultures were negative. The Wassermann and Kahn reactions of the blood were negative. Cultures of material from the nose and throat were negative for diphtheria bacilli. The urine contained small amounts of albumin and an occasional cast. On the day after admission the temperature rose to 104 F. It reached 108 F. on the following day and thereafter remained elevated between 102 and 106 F. until the child died, on the eighth day of residence.

Autopsy showed externally the lesions of chickenpox in various stages of regression. All the internal organs were normal, with the exception of the lungs,

which showed a moderate hypostatic pneumonia. The scalp, calvarium and dura mater appeared normal. The brain was large, weighing 1,450 Gm., and its convolutions were slightly flattened. There was an increased quantity of fluid in the subarachnoid spaces. On serial section the brain revealed no focal lesions, although the lenticular nuclei seemed swollen and edematous.

Detailed microscopic study failed to reveal any of the lesions reported by Zimmerman and Yannet or by Van Bogaert. It must be remembered that the disease in my case was chronic, lasting fully a month. The ganglion cell changes were inconspicuous. Occasionally, shrinking of the cytoplasm was seen, but this was not marked. An artery with a perivascular collar of red blood cells was occasionally seen in the white matter. Also, a few blood vessels showed perivascular collars of mononuclears. The meninges presented slight changes. As a whole, the lesions in this case were meager and tend to illustrate that anatomic lesions are often not comparable to the clinical symptoms. It is probable that there is no constant pathologic picture in the nervous system in encephalitis following chickenpox.

Encephalitis Following Dysentery.—The autopsy reports on the cerebral lesions in dysentery are few. Lenhartz [52] gave a careful clinical review of this type of encephalitis. In 1930, Buttenwieser [53] reported a fatal case in which positive agglutination was obtained for the Shiga-Kruse bacillus. At autopsy he observed many petechiae throughout the cerebral cortex, the basal ganglions and the region of the aqueduct. In the centers of most of these hemorrhages there were small blood vessels. A detailed description of the pathologic lesions was not given.

Encephalitis Following Typhus.—Lesions of the brain in encephalitis following typhus have been described by Ceelen,[54] Herzog,[55] Fraenkel,[56] Jarisch,[57] Feldmann,[58] Grodzki,[59] Spielmeyer [60] and Hassin.[61] Except in a few minor details, their descriptions agree fairly well.

Grossly, the brain may appear edematous and hyperemic (Herzog). The meninges usually show mononuclear invasion, as described by Hassin and Jarisch, although Grodzki found purulent meningitis in his case. In the brain parenchyma inflammatory and degenerative changes occur. The former consist in mononuclear infiltration of the walls of blood vessels the size of precapillaries and capillaries. The blood vessels contain thrombi, and the round cell infiltrate usually fills the lymph

52. Lenhartz, H.: Klin. Wchnschr. **20**:312, 1883.
53. Buttenwieser, S.: München. med. Wchnschr. **67**:1472, 1920.
54. Ceelen: Klin. Wchnschr. **20**:530, 1916.
55. Herzog, G.: Centralbl. f. allg. Path. u. path. Anat. **29**:97, 1918.
56. Fraenkel, E.: München. med. Wchnschr. **61**:57, 1914.
57. Jarisch, A.: Deutsches Arch. f. klin. Med. **126**:270, 1918.
58. Feldmann, P. M.: J. A. M. A. **87**:886, 1926.
59. Grodzki, A. B.: München. med. Wchnschr. **76**:709, 1929.
60. Spielmeyer, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **46**:1, 1919.
61. Hassin, G. B.: Arch. Neurol. & Psychiat. **11**:121, 1924.

space of Virchow and Robin. As a rule, no polymorphonuclears are seen. Fraenkel reported marked necrosis of the walls of the vessels, which would account for the formation of thrombi. However, this observation was vigorously denied by Spielmeyer.

The degenerative changes are characteristic and consist in infiltration of the ganglion cells by lipoids, as well as a mild diffuse and a marked focal glial proliferation, the latter forming small nodules which are called by many authors "typhus bodies."

The ganglion cells show changes varying from slight swelling of the cells to complete disintegration with karyorrhexis of the nuclei and marked infiltration of the cell body by lipoid. Jarisch observed no alteration in the nerve cells. The typhus bodies consist of foci of cells measuring from 0.04 to 0.15 mm. in diameter, usually not circumscribed. These nodules are prominent in the basal ganglions, the cortex, the midbrain, the medulla, the cord and the cerebellum. The foci are usually found in relation to a blood vessel of the precapillary or capillary type. They are composed of mononuclear cells probably of glial origin, although Ceelen expressed the belief that they are of vascular origin. Occasionally a few polymorphonuclears are present in these nodules. According to Hassin, these typhus bodies are not specific for typhus fever, being found also in epidemic encephalitis and poliomyelitis; however, in neither of these conditions are they as numerous as in typhus. Mooser, in experiments on guinea-pigs, noticed that these bodies never appeared before the fourth day following infection but that they were numerous thereafter. In only a single case—one reported by Herzog—was there any mention made of petechial hemorrhages in the brain. Most authors deny the occurrence of such lesions.

Postvaccinal Encephalitis.—This is a striking disease complex. It was first described in Holland by Bastiaanse in 1924. Since then many cases have been reported from almost all the countries where vaccination is practiced. Flexner,[62] Rivers[63] and Scott[64] gave good statistical reports of the occurrence of this disease. From 1922 to 1928, 93 cases were reported in England and 150 cases in Holland. In England the ratio of encephalitis to vaccination is 1: 50,000, while in Holland it is 1: 5,000. In England most of the vaccinating is done during infancy, while in Holland it is done during the school years. Although the reports indicate that the condition is fairly rare in infants, Scott was able to collect 22 instances of postvaccinal encephalitis in infants, with a mortality of 54.5 per cent. These cases occurred in England, Holland, Germany, France and Sweden.

62. Flexner, S.: J. A. M. A. **94**:305, 1930.
63. Rivers, T. M.: J. A. M. A. **92**:1148, 1929.
64. Scott, T. F. M.: Brit. J. Child. Dis. **27**:245, 1930.

Clinical studies of this type of encephalitis have been reported by Heckman,[65] Huber,[66] Gildemeister,[67] Gordon and Rhea,[68] Fulgham and Beykirch,[69] Flexner [62] and Wilson and Ford.[46] Its manifestations are typical: a hyperacute course, a high mortality and complete recovery of the patients who survive. The most common prodromal symptoms are headache, vomiting and pyrexia. The onset is sudden, and the symptoms are alarming. Consciousness is quickly lost; the temperature rises to alarming heights, and profound prostration and paralysis set in. Stiffness of the neck and a positive Kernig sign are uncommon. The tendon reflexes are usually lost. There are retention of urine and constipation. Death ensues in one third of all the cases on the sixteenth to the eighteenth day but often occurs as early as the second day. In all the cases there is a history of recent vaccination, with normal progress. Scott [64] divided the types of postvaccinal encephalitis into five clinical groups:

1. The meningeal type, with vomiting, headache and stiff neck, but with few convulsions.

2. The cortical type, with convulsions as the chief symptom.

3. The brain stem type, with drowsiness, ocular palsies, facial palsies and tonic movements of the limbs.

4. The tetanus type, with opisthotonos of the limbs.

5. The lower motor neuron type, resembling anterior poliomyelitis.

The lesions of this complex have been described by Flexner,[62] Wilson and Ford,[46] Perdrau,[70] Turnbull and McIntosh,[71] Denson [72] and Gordon and Rhea.[68] All these authors agree as to the principal lesions which involve both the gray and the white matter of the brain and spinal cord. There is congestion of the meninges, but rarely flattening of the convolutions. A few red spots may be seen on the surface of the cord.

Microscopically, most of the small blood vessels of the brain are surrounded by collections of lymphocytes and plasma cells, as well as by cells with elongated nuclei resembling fibroblasts. These cells lie chiefly in the adventitial sheath of the vessels. Small areas of demyelinization are seen about many vessels which do not show the inflammatory infiltrations. Often these areas of perivascular softening present

65. Heckman, J.: J. A. M. A. **93**:1851, 1929.

66. Huber, H. G.: Deutsche med. Wchnschr. **55**:1370, 1929.

67. Gildemeister, E.: Deutsche med. Wchnschr. **55**:1372, 1929.

68. Gordon, A. H., and Rhea, L. J.: Am. J. M. Sc. **184**:104, 1932.

69. Fulgham, J. H., and Beykirch, J. G.: J. A. M. A. **92**:1427, 1929.

70. Perdrau, J. R.: J. Path. & Bact. **31**:17, 1928.

71. Turnbull, H. M., and McIntosh, J.: Brit. J. Exper. Path. **7**:181, 1926.

72. Denson, T. L.: Texas State J. Med. **28**:292, 1932.

many fat granule cells. The axis-cylinders are as a rule intact. Ganglion cells are but little involved, and hemorrhages are rarely seen.

Encephalitis and Neuritis Following Vaccination Against Rabies.—This disease is believed to be due to some component of the suspensions used in the vaccination which in peculiarly susceptible persons acts on the peripheral nerves, the cord or the brain. The symptoms vary from simple neuritis (with involvement of one or more nerves, most commonly the facial, oculomotor, vagus, radial or sciatic nerve) with little or no motor paralysis to acute ascending paralysis of the Landry type, with sudden onset, headache, fever, restlessness, paralysis of the legs, sphincter disturbances, pain in the back and face, bulbar paralysis and death in more than half the cases (Fielder [73] and Bassoe and Grinker [74]).

Remlinger [75] reported 529 cases in 1,164,264 patients treated. Stuart and Krikorian [76] recorded 39 "accidents" in 6,764 cases prior to 1915. These complications are infrequent in children and more common in men than in women. The onset is usually from ten to twenty days after the first treatment. In many cases the dogs proved to be nonrabid; hence the disease must be due to some constituent of the vaccine.

The most severe changes are in the spinal cord, although some damage also occurs in the brain. Jochmann [77] described changes in the cord similar to those in measles and smallpox. There were edema and necrosis of the tissues around the vessels, with a slight infiltration by round cells. There was disappearance or degeneration of the large nerve cells in the gray matter. No Negri bodies were seen.

Stuart and Krikorian, in their excellent report in 1928, described changes in both the gray and the white matter of the cord similar to those recorded by Jochmann. Most investigators are agreed that hemorrhagic lesions are rare. Busson,[78] however, reported a case with punctate capillary hemorrhages in the medulla and cord.

ENCEPHALITIS SECONDARY TO SOME EXOGENOUS POISON

Encephalitis Following Lead Poisoning.—Numerous cases of encephalitis following lead poisoning in man, as well as experimental lead intoxication in animals, have been reported. Kato [79] completely reviewed the Japanese literature on this subject and added many new instances. In spite of the investigations on animals and the study of human material, agreement as to the lesions in this type of cerebral

73. Fielder, F.: J. A. M. A. **66**:1769, 1916.
74. Bassoe, P., and Grinker, R.: Arch. Neurol. & Psychiat. **23**:1138, 1930.
75. Remlinger, P.: Ann. Inst. Pasteur **17**:834, 1903.
76. Stuart, G., and Krikorian, K.: Ann. Trop. Med. **22**:327, 1928.
77. Jochmann, G.: Deutsche Ztschr. f. Nervenh. **47**:267, 1913.
78. Busson, B.: Centralbl. f. Bakt. (Abt. 1) **99**:80, 1926.
79. Kato, K.: Am. J. Dis. Child. **44**:569, 1932.

involvement is still lacking. Friedländer [80] observed no alterations in the brain of his patient, while Cadwalader,[81] Lehmann, Spatz and Wisbaum-Neubürger [82] and McCarthy [83] reported striking changes in the nerve cells in the brain of both men and animals who died of lead poisoning.

Lehmann, Spatz and Wisbaum-Neubürger experimented with cats, in which they caused what they described as liquefaction of all the nerve cells, with destruction of both the nucleus and the cell body. McCarthy produced cerebral lesions in dogs with lead acetate and noted extensive chromatolysis and vacuolation of the nerve cells, with slight glial proliferation. Somewhat similar changes were reported by Cadwalader in human material. Hassin,[84] however, in 3 cases found the nerve cells uninvolved. He noted only thickening of the pia-arachnoid and slight glial proliferation. Barron and Habein [85] reported a case of encephalitis following lead poisoning, in which the brain was normal. McKhann and Vogt [86] suggested that many of the symptoms of encephalitis following lead poisoning may be due to increased intracranial pressure and not to destruction of nerve cells.

Recently, I [87] described a case of encephalomyelitis in a 53 year old man who was thoroughly exposed to lead paint for seven months. A study revealed marked destruction of the nerve cells in the cerebral cortex (fig. 2) and extensive demyelinization of the posterior and lateral columns in the spinal cord.

Encephalitis Following Arsenic Poisoning.—Since the introduction of arsenicals, the incidence of cerebral arsenical lesions has increased. The lesions are usually hemorrhagic, and for this reason encephalitis following arsenic poisoning has often been called "hemorrhagic purpura." In 1933, Globus and Ginsburg [88] found reports of 74 cases with complete autopsy, although numerous cases less completely studied have been reported (Almkvist,[89] Hahn,[90] Nonne,[91] Pritzi [92] and Mingazzini [93]).

80. Friedländer, C.: Virchows Arch. f. path. Anat. **75**:24, 1879.
81. Cadwalader, W. B.: J. Nerv. & Ment. Dis. **39**:153, 1912.
82. Lehmann, K. B.; Spatz, H., and Wisbaum-Neubürger, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **103**:323, 1926.
83. McCarthy, D. J.: Univ. Pennsylvania M. Bull. **14**:398, 1902.
84. Hassin, G. B.: Arch. Neurol. & Psychiat. **6**:268, 1921.
85. Barron, M., and Habein, H. C.: Am. J. M. Sc. **162**:833, 1921.
86. McKhann, C. F., and Vogt, E. C.: J. A. M. A. **101**:1131, 1933.
87. Baker, A. B.: Am. J. Path. **10**:637, 1934.
88. Globus, J. H., and Ginsburg, S. W.: Arch. Neurol. & Psychiat. **30**:1226, 1933.
89. Almkvist, J.: München. med. Wchnschr. **58**:1808, 1911.
90. Hahn, R.: München. med. Wchnschr. **67**:1222, 1920.
91. Nonne, M.: Deutsche Ztschhr. f. Nervenh. **94**:158, 1926.
92. Pritzi, O.: Zentralbl. f. Gynäk. **52**:2930, 1928
93. Mingazzini, G.: Deutsche Ztschr. f. Nervenh. **103**:1, 1928.

A 21 year old white woman was admitted to the hospital unconscious. She had recently been exposed to syphilis, and eleven days before admission she had received 0.6 Gm. of neoarsphenamine intravenously, which was followed six days later by a similar injection. Two days afterward she suddenly had a severe headache, lost appetite, and became lethargic. The following day she was more listless and had generalized convulsions. There was marked rigidity of the neck, and a tentative diagnosis of meningitis was made. On admission she was comatose; the neck was rigid, and the blood pressure was 130 systolic and 80 diastolic. A confluent macular eruption covered the arms and shoulders. The temperature was 102 F. It rose rapidly to 106 F., where it remained until the patient's death, which occurred on the second day in the hospital.

At autopsy the body showed mottling of the lateral surface of the right shoulder, the right arm and the left hip with tiny closely-set petechial hemorrhages. The

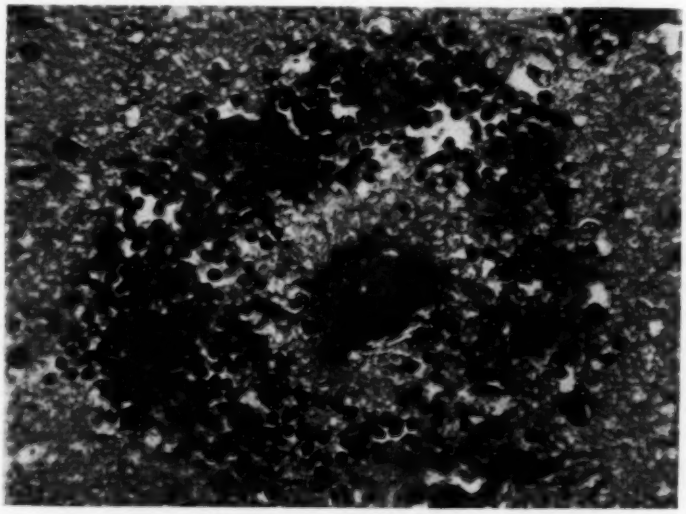


Fig. 2.—Photomicrograph of a section through the cerebral cortex of a patient with lead encephalomyelitis. Note the marked shrinking and irregularity of the nerve cells. Hematoxylin and eosin stain; magnification, × 400.

walls of the heart and bladder walls contained a few petechiae. Coronal sections through the brain revealed numerous small hemorrhages. In the white substance at the lateral inferior margin of the putamen on both sides there were softened areas 2.5 by 1.5 cm., surrounded by numerous hemorrhages. In the anteromedial portion of both temporal lobes in the region of the uncus and amygdaloid nuclei were other slightly softened areas surrounded by densely packed petechiae. Many hemorrhages were present on the inferior surface of the corpus callosum, on the superior and lateral walls of the lateral ventricles and in the posterior portions of the brain.

The most characteristic microscopic feature was the numerous hemorrhages throughout the white substance (fig. 3), varying in size and extending occasionally only into the perivascular spaces, but more often involving the surrounding tissue. A few lymphocytes and polymorphonuclears were present within the hemor-

rhages. Numerous small hemorrhages were also observed in the cerebral cortex. Many of the blood vessels showed endothelial swelling, as well as a hyalinization of the walls. Numerous vascular walls were infiltrated by polymorphonuclears and lymphocytes. In the vessels hyaline or cellular thrombi that completely filled the lumen were frequent (fig. 3). There was no destruction of brain tissue about the periphery of the hemorrhages. No reaction was observed on the part of the neuroglia or the microglia. The large nerve cells were intact.

The lesions in this case correspond with those reported in the literature. Thrombosis of vessels appears to be a common occurrence (Pritzi,[92] Wechselmann,[94] Scott and Moore,[95] von Marschalko and Vespremi [96] and others). The question of localization of the hemorrhages in the white substance of the brain is somewhat unsettled. In my case

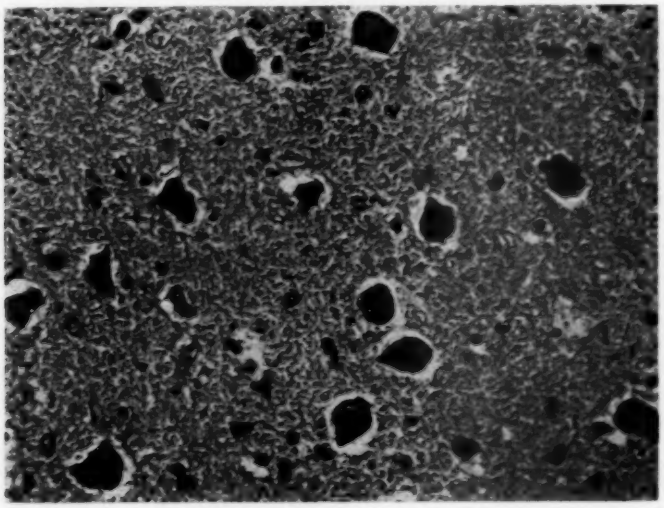


Fig. 3.—Photomicrograph showing petechia in the brain of a patient who died of arsenic poisoning. The hemorrhage is of the ring type. The solid dark area in the center of the hemorrhage is a thrombosed vessel. Azo-carmine stain; magnification, × 400.

extravasations were observed also in the cerebral cortex. This is in agreement with the observations of Almkvist [89] and Post,[97] although others have detected them only in the white substance. Nonne [91] and Mingazzini [93] reported hemorrhagic lesions in both the gray and the white matter of the cord.

94. Wechselmann, W.: München. med. Wchnschr. **64**:345, 1917.

95. Scott, E., and Moore, R. A.: Am. J. Syph. **12**:252, 1928.

96. von Marschalko, T., and Vespremi: Arch. f. Dermat. u. Syph. **112**:813, 1912.

97. Post, C. D.: Am. J. Syph. **11**:444, 1927.

Encephalitis Following Phosphorus Poisoning.—Cerebral symptoms following phosphorus poisoning are infrequent. Spielmeyer [60] was one of the first to describe cerebral hemorrhages in phosphorus poisoning. Wertham,[98] in reviewing the literature, pointed out that by far the most frequent lesion is destruction of the nerve cells. Vascular injury with bleeding is rare.

Encephalitis Following Alcohol Poisoning.—Acute and chronic alcohol poisoning seems to produce definite injury to the central nervous system. Cerebral hemorrhages are occasionally present in patients dying of alcoholism, an observation which was first made by Wernicke in 1881. More recently, Bender and Schilder [99] described 7 cases in which the patients came to autopsy. The lesions occurred in parts of the central nervous system adjacent to the spinal fluid spaces, such as the surface of the ventricles and of the brain and brain stem. Often the substantia nigra, the subthalamic and thalamic regions and the putamen were involved. Nuclear tissue was more prone to injury than the adjacent myelinated areas. The lesions were characterized by glial reaction, chiefly of astrocytes; proliferative changes in small blood vessels, and hemorrhages. Nerve cell changes were absent.

Marchiafava [100] and Italian workers believed that certain alterations may be present in the brain, which from their location may be judged as specific for chronic alcoholism. This alteration is degeneration of the gray substance in the corpus callosum and the anterior commissure. In the corpus callosum the degeneration extends from the genu to the splenium. Often there is also injury to the two middle cerebral peduncles and to the white substance under the cortex of the cerebral hemispheres.

SUMMARY

From a strict neuropathologic point of view, the various alterations in the central nervous system may be divided into two large groups, namely, the inflammatory lesions and the degenerative lesions. The criteria of cerebral inflammation are changes in which a variety of free and fixed cells participate. The mobile infiltrating cells are the polymorphonuclears, lymphocytes, plasma cells and scavenger cells. The latter participate in the removal of the degenerated myelin. The fixed cells in the usual inflammatory processes of the central nervous system are the glia cells, the function of which is scar formation and repair. The degenerative changes consist chiefly in alterations of the ganglion cells, demyelinization of nerve fibers and vascular injury and hemorrhage. In the latter there are secondary reactions on the part of the

98. Wertham, F.: Arch. Neurol. & Psychiat. **28**:320, 1932.

99. Bender, L., and Schilder, P.: Arch. Neurol. & Psychiat. **29**:990, 1933.

100. Marchiafava, E.: Proc. Roy. Soc. Med. **26**:1151, 1933.

glial fibers and microglia similar to those in inflammation, making sharp differentiation between the degenerative and inflammatory lesions difficult.

It is apparent, therefore, that the central nervous system can react in but a limited manner to various irritants and that the structural pictures in the different types of encephalitis must present a certain degree of overlapping. Nevertheless, there is a predominance of certain changes in certain diseases, such as: infiltration by perivascular mononuclears, in epidemic encephalitis, including the St. Louis type, and in herpetic encephalitis and encephalitis following mumps; perivascular demyelinization, in encephalitis following measles, smallpox, chickenpox and vaccination against rabies and smallpox; nerve cell destruction, in encephalitis following herpes, whooping cough, chickenpox and poisoning with lead and phosphorus, and cerebral hemorrhages, in hemorrhagic encephalitis and arsenic intoxication.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Gotthelf Carl Huber, professor of anatomy in the University of Michigan and dean of the graduate school, died on December 26, at the age of 69. He graduated in medicine in 1887 and was a member of the faculty for forty-five years. He was the chairman of the Medical Fellowship Board of the National Research Council.

Frederick G. Novy, professor of bacteriology in the University of Michigan since 1902 and dean of the medical school, will retire from active service next February.

Geoffrey Hadfield of the University of Bristol has been appointed professor of pathology in the University of London (St. Bartholomew's Hospital Medical College).

Theobald Smith, director of the department of animal pathology of the Rockefeller Institute for Medical Research until recently, died on December 10, at the age of 75. An extended sketch of the work and personality of this great investigator will appear later.

According to *Science*, Charles Norris has been given a gold medal by the New York Academy of Medicine for "his outstanding work in forensic medicine." Dr. Norris has been chief medical examiner of New York City since 1918.

Katherine W. Dewey, associate professor of clinical pathology in the school of dentistry in the University of Pittsburgh, formerly assistant professor of oral pathology in the college of dentistry in the University of Illinois and at one time fellow in pathology in Rush Medical College, has died at the age of 66.

Society News.—The Tenth International Congress of the History of Medicine will be held in Madrid, Spain, from Sept. 23 to 29, 1935.

Graduate Study in Forensic Medicine.—Two courses of graduate study have been outlined by the department of forensic medicine in University and Bellevue Hospital Medical College, New York, and are scheduled to begin early in 1935. One is a continuation of the long course begun in 1934, which covers a period of from three to five years. The second is a shorter course primarily for coroners' physicians or for those who wish to prepare themselves for such work and is open to graduates of approved medical schools. Formal instruction, occupying the morning hours during two semesters of five months each, will include conferences and work in the laboratories of the chief medical examiner of New York City.

Obituary

THEOBALD SMITH, M.D.
1859–1934

The son of Philip and Theresa Kexel Smith, Theobald Smith was born in Albany, N. Y., on July 31, 1859, and died in New York City on Dec. 10, 1934. He was graduated from Cornell University in 1881 with a Ph.B. degree and received an M.D. degree from the Albany Medical School in 1883.

He at once engaged in medical research, his first publication appearing the year of his graduation in medicine, and throughout life he continued as a professional investigator of disease, more especially of disease produced by parasites. The continuity of his effort appears in the fact that during his scientific career of more than one-half century no year passed without a contribution of one or more scientific publications.

In 1884, Smith was appointed to the United States Department of Agriculture and served in its Bureau of Animal Industry until 1895, first as assistant and then as chief of the division. During his residence in Washington, Smith acted also as lecturer and professor in the medical department of Columbian University, now George Washington University.

In 1895, Smith resigned from the federal service to accept an appointment in Harvard University as professor of applied zoology. One year later the title of his chair was changed to that of professor of comparative pathology and in this position Smith continued his work at Harvard until 1914. He was exchange professor from Harvard University to the University of Berlin in 1911 and 1912.

Throughout the nineteen years of his connection with Harvard, Smith was active in the Massachusetts State Board of Health, serving as director of the antitoxin and vaccine laboratory and as pathologist.

In 1914, Smith resigned from Harvard University to join the Rockefeller Institute for Medical Research as director of its newly established department of animal pathology at Princeton, N. J. For fifteen years he continued active direction of that department, until in 1929, at the age of 70, he retired as director, to continue his investigation for the remaining five years of his life as a member emeritus of the institute.

Apart from a consideration of his particular researches, the eminence of Theobald Smith as a man of science is attested by the fact that he received honorary degrees from twelve universities, was a member of twenty-five learned societies and was the recipient of twelve medals, including the Copley medal.

In any consideration of the individual scientific contributions of Theobald Smith, several investigations appear of outstanding importance, namely, those which relate to the rôle of intermediate hosts in the transmission of infections, to immunization with killed bacteria, to the differentiation of varieties of tubercle bacilli, to the experimental production of disease by diet deficiency, to immunization with mixtures of toxins and antitoxins and to the establishment of animal hypersensitiveness to proteins.

Each of these contributions was basic in establishing a principle the subsequent application of which marked an epoch in medical science.

The demonstration that in the Texas fever of cattle a tick acting as an intermediate host transfers the causal parasite from one bovine host to another not only furnished the means of eliminating Texas fever but initiated the recognition of the disease-propagating rôle of intermediate hosts in general. This led directly to an understanding of the mode of extension of important diseases of man, such as malaria, yellow fever, African sleeping sickness and Rocky Mountain spotted fever, by Ross, Reed, Bruce, Ricketts and others.

In 1886, Smith, collaborating with D. E. Salmon, presented the first proof that killed bacteria may be used to induce active immunity in experimental animals. These findings led directly to the prevention of disease in man. They established the basis for the development of protective vaccination against typhoid fever, paratyphoid fever and cholera as practiced today.

Prior to 1896 there had been no challenge of the position held by Koch that all mammalian tuberculosis was caused by one and the same tubercle bacillus. In that year, however, Smith drew attention to marked differences existing between tubercle bacilli cultivated by him from a tuberculous bull and those from a pet bear, presumably infected from its tuberculous master. Two years later (1898), Smith, in an extension of this work, took the definite stand that tuberculosis commonly occurring in cattle is caused by a tubercle bacillus distinct in type from the tubercle bacillus commonly producing tuberculosis in man. So explicit were the findings of Smith that Koch withdrew from his previous position and in 1901 publicly accepted the differentiation of a bovine and a human type of tubercle bacilli.

This determination that the tuberculosis of cattle is not the tuberculosis of man not only brought Theobald Smith world-wide recognition as an investigator but at once exerted profound effect on the methods employed in the prevention of human tuberculosis.

It is worth recording that in his initial study of the two strains of tubercle bacilli, Smith established practically all of the criteria known today for distinguishing bovine from human tubercle bacilli.

In 1894, Smith induced what appears as the first experimental production of disease due to vitamin deficiency. This work, which has received but slight notice, was included in a publication on swine ery-

sipelas in the Annual Reports of the United States Bureau of Animal Industry, 1895-1896. On page 172, Smith stated that for several years he had observed that guinea-pigs fed bran and oats but deprived of grass and "succulent vegetables, such as cabbage," succumbed in from four to eight weeks to "a peculiar disease, chiefly recognizable by subcutaneous extravasation of blood." In confirming these observations, he segregated two groups of guinea-pigs. To one group he fed a mixture of bran and oats and also cabbage. The second group received the bran and oats but no cabbage. The result was thus stated: "While those fed with cabbage survived, those not fed with it died. . . . The outcome of the experiment demonstrates the fatal result following the abstraction of green food."

This experimental production of scurvy in guinea-pigs preceded by ten years the next experiments relating to disease causation by vitamin deficiency.

In 1909, Smith presented extensive quantitative experiments concerning the production of active immunity to diphtheria toxin by the injection of toxin-antitoxin mixtures. He established not only the efficiency but the safety of the procedure and recommended its use in man as a prophylaxis for diphtheria. The adoption of the suggestion by others, notably von Behring and Park, has resulted in the almost complete elimination of diphtheria in communities in which this method of preventive immunization has been generally practiced.

In 1904, Smith observed that guinea-pigs once given an injection of horse serum reacted violently to a second injection of the serum, displaying a symptom complex never occasioned by the first injection. He established the phenomenon as one occurring with regularity. Smith, himself, recognized more clearly than many workers who followed him that the anaphylactic reaction is an in vivo display of an antibody-antigen reaction. In describing the phenomenon to Ehrlich, he referred to it as "simply in wholesale what the Arthus phenomenon is in retail." In the same conversation he stated that, the principle being established, he had no intention of continuing experiments in this line and suggested that some one in Ehrlich's laboratory extend the work. Otto was designated by Ehrlich, and after conference with Smith, Otto began at once his experimental study, which was published in 1905 under the caption "the Theobald Smith Phenomenon." In the thirty years which have followed, no other topic of immunology has received the attention given to the induced hypersensitiveness to proteins demonstrated by Smith, and certain human diseases have been identified as displays of such hypersensitiveness. The full significance of the phenomenon of anaphylaxis, however, remains undetermined, the fundamental physiology of its production being unknown.

Important as are the aforementioned works, citation of them is but meager recognition of the contributions of Theobald Smith. The tremendous volume of his work is recorded in 247 scientific publications

dealing with disease in man and in domesticated animals. The accuracy in observation and the exactness in experimentation with which these researches were conducted combined with the explicitness of publication guarantee a worth beyond contemporary evaluation. The most unnoticed of these findings may in a future setting appear as basic as does now the observation concerning food deficiency as a cause of disease after surviving an obscurity of over forty years.

By coincidence, the last of Smith's publications was a general treatise on parasitism and disease, which places in context a great mass of his individual findings and discloses the general perspective in which he viewed them.

No marshaling of the technical results obtained by him may be offered in full acknowledgment of the worth of Theobald Smith to science. Here, not only the work but the example of the worker in its doing constitutes a contribution. The example is that of independent, continuous, unhurried study of natural phenomena for five decades with unostentatious efficiency and the registration of results without the clamor of heralding.

Theobald Smith was a man of conviction, and his conviction embraced the belief that the honest and intelligent search for the truths of nature guaranteed ultimate benefits to mankind and joy to the searcher.

His methods of investigation were those both of the naturalist and of the experimenter: He combined acute powers of observation with mastery of detail in exact experimentation. His topics of investigation were suggested more by occurrences in nature close at hand than by the contemporary activities of other investigators. He was given more to the establishment of fact than to the elaboration of theory. At one point he stated: "Science gnaws irregularly away at the lump of the unknown, and the undigested portions are temporarily bridged over by theories." At another point he referred to "hypotheses being largely scaffolding for furnishing a foothold in building up facts."

His idealism and vision require no emphasis beyond the quotation of a letter in reply to the request of a colleague (Krumbhaar) for a statement of his attitude in research for the inspiration and guidance of younger men:

> As we grow old we come to the end of an individual era in which we have tried "to do our part." We begin to realize the important function of the past in shaping the future. We also feel the at times benumbing and soporific effects of that past to be gotten rid of.
>
> It is not uncommon for the younger generation to criticize or even disregard earlier work because it is not complete from the more recent standpoint. No research will answer all queries that the future may raise. It is wiser to praise the work for what it has accomplished and then to formulate the problems still to be solved. It is not profitable to enter into controversies, especially with those working in another geographic area or continent unless the material on which their researches are based has been examined.

To those who have the urge to do research and who are prepared to give up most things in life eagerly pursued by the man in the street, discovery should come as an adventure rather than as the result of a logical process of thought. Sharp, prolonged thinking is necessary that we may keep on the chosen road but it does not itself necessarily lead to discovery. The investigator must be ready and on the spot when the light comes from whatever direction.

There are many to compete with the young investigator. Opportunities for research have been increased a hundred fold in the past half century. More and more our colleagues fail to understand our work because of the high specialization of research problems. We must not be discouraged if the products of our labor are not read or even known to exist. The joy of research must be found in doing since every other harvest is uncertain and even the prizes do not always go to the discoveries to which we would assign them. Research has deserted the individual and entered the group. The individual worker finds the problem too large, not too difficult. He must learn to work with others.

In bacteriology and pathology research is slowly receding from the ultra-practical point of view of the early leaders. One group thought it possible to catch all bacteria in transit from one victim to another and to suppress disease in this way. Another group thought that a vaccine could be prepared for every disease. We have learned much since then and have become quite humble. Our researches no longer lead straight to Public Health regulations. They are more elusive and difficult to fit into any scheme for decreasing the incidence of disease. We must be content with the vision of future usefulness.

In general, a fact is worth more than theories in the long run. The theory stimulates but the fact builds. The former in due time is replaced by one better but the fact remains and becomes fertile. The fertility of a discovery is perhaps the surest measure of its survival value.

What is one man's meat is another's poison in research as in other vocations. Temperament goes far towards deciding our course. In the three different environments in which I have spent my active life I have always taken up the problems that lay spread out before me in the new environment, chiefly because of the easy accessibility of material without which research cannot go on; for in the early years material and resources were exceedingly scant and this meagerness determined the direction and scope of all research. My interest in a problem usually lagged when certain results could be clearly formulated or practically applied. To continue and analyze still further every link of the established chain either failed to hold my interest or was made difficult or impossible for causes lying outside the problem. As I look back it is precisely these links that have provided innumerable problems to others. Each link has grown into a chain and the end of successive chain making is not in sight.

The intellectual power of Smith in straight thinking, visualization and memory requires no especial comment; for those not acquainted with his work, it would be of no import, and for those with such acquaintance, superfluous.

A modest, quiet, dignified, busy man, he did not spread his companionship too thin, but to those for whom it was reserved it brought full measure of enthusiasm, sympathy, humor, enlightenment and love.

By some and, perhaps, by many, Theobald Smith will be regarded as the most notable figure in American medicine of his period.

PRESTON KYES.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

BILE PIGMENT AND HEMOGLOBIN REGENERATION. ARTHUR J. PETEK AND GEORGE R. MINOT, Am. J. M. Sc. **188**:206, 1934.

Nine selected patients with chronic hypochromic anemia were studied to determine whether bile pigment could assist in the production of hemoglobin. Concentrated bile pigment alone caused not a reticulocyte response, but an increase of hemoglobin, about 7 per cent in ten days. This indicates that in certain anemic patients bile pigment for building hemoglobin can be absorbed from the gastrointestinal tract. After a reticulocyte response to a suboptimal dose of iron occurred, bile pigment was fed directly with the same dose of iron, and there followed a second reticulocyte response. The second response was sometimes of greater magnitude than the first. This indicates that bile pigment, in some unknown manner, can facilitate either the absorption or the utilization of iron. One patient who could not in fourteen months obtain a normal hemoglobin level with large daily doses of iron promptly showed an increase in the concentration of hemoglobin when bile pigment was fed in addition to iron. It is suggested that in certain cases of hypochromic anemia there may be, in addition to iron deficiency, a deficiency of useful material that is contained in bile pigment.

AUTHORS' SUMMARY.

EXPERIMENTAL DYSENTERY. G. M. DACK AND E. PETRAN, J. Infect. Dis. **55**:1, 1934.

Bacterium dysenteriae (Flexner) was inoculated into isolated loops of the colon in two adult monkeys (Macacus rhesus). A freshly isolated virulent strain of the organism produced an infection in these loops resulting in a profuse discharge of bloody mucus. A marked systemic reaction accompanied the infection in the loops of bowel, the monkeys showing pallor, loss of appetite, leukopenia, loss of weight and prostration. The acute symptoms appeared within forty-eight hours and lasted from three to four days. Within a week the discharge from the fistulas had ceased, and the systemic symptoms had disappeared. Agglutinins developed in the serum of these animals for Bact. dysenteriae (Flexner), but not for strains of Bacterium coli which were resident in the segments of bowel. At no time during the course of the infection in the isolated loops of colon was there evidence of infection in the portion of the colon through which the fecal stream passed. Organisms resident in the isolated segments of bowel before introduction of the dysentery bacilli remained in considerable numbers throughout the course of the infection. Severe symptoms of dysentery developed in two large adult monkeys (Macacus rhesus), which were fed organisms of the same strain; one of them died on the second day after being fed this culture.

FROM THE AUTHORS' SUMMARY.

SUBTOTAL RESECTION OF THE PANCREAS FOR HYPOGLYCAEMIA. E. A. GRAHAM AND A. F. HARTMANN, Surg., Gynec. & Obst. **59**:474, 1934.

The report deals with the effects of surgical resection of between 80 and 90 per cent of the pancreas of a 1 year old child who suffered from chronic hypoglycemia, repeated convulsions and marked mental retardation. A temporary hyperglycemia followed the removal of so much of the pancreas, but later the blood sugar returned to a normal level while the symptoms referable to hypoglycemia promptly disappeared and had not returned after a period of nine months. Histologically the

pancreatic tissue was essentially normal, and it remains uncertain whether the hypoglycemia was due to hyperinsulinism or to some other factor. In contrast to other instances of partial resection, almost all of the pancreas was removed in this case. There was no interference with the general nutrition or disturbance of the acid-base balance following the resection.

FROM THE AUTHORS' SUMMARY (W. C. HUNTER).

CHOLINE AND LIVER FAT. D. L. MACLEAN AND C. H. BEST, Brit. J. Exper. PATH. **15**:193, 1934.

With descriptions, photomicrographs and colored drawings (Sudan III), the authors demonstrate marked fatty infiltration and degeneration in the livers of diabetic dogs receiving fat in their diets and of normal rats receiving diets high in fat or cholesterol, but absence of such deposition of fat in the livers when adequate amounts of choline were added to the experimental diets. There is no evidence that choline affects the phagocytosis of fat particles. In some as yet unexplained way, choline prevents the deposition of fat in the livers of diabetic dogs or normal rats under the conditions of these experiments.

JAMES R. MACK.

HYPERVITAMINOSIS D RICKETS: THE ACTION OF VITAMIN D. ARTHUR W. HAM AND MURRAY D. LEWIS, Brit. J. Exper. Path. **15**:228, 1934.

Young rats receiving large daily doses of vitamin D showed rachitic lesions in their long bones after three weeks. As the matrix which formed in the bones during the experiment was poorly calcified, it was concluded that the administration of large amounts of vitamin D inhibited the normal calcification in these bones. As osteoclasts did not form a prominent part in the histologic picture, the poor calcification could not be attributed to them. The phenomena observed can be explained best, it is thought, by the theory that vitamin D in some way increases the attraction of the blood for calcium. The results are compatible with, although they do not directly support, the theory that vitamin D acts through the intermediary of the parathyroid mechanism to control a fraction of the serum calcium.

AUTHORS' SUMMARY.

PARTICIPATION OF PERIPHERAL NERVES IN ALLERGIC TISSUE REACTIONS. J. M. LASOWSKY AND M. M. KOGAN, Virchows Arch. f. path. Anat. **292**:428, 1934.

Rabbits were sensitized by five or six subcutaneous injections of normal horse serum given at the rate of one every five to six days. The sensitized animals then received an injection of horse serum into the muscles of the calf of the hind-leg. The animals were killed at variable intervals, and the muscle which had received the injection and the tibial and sciatic nerves were examined histologically. For controls, horse serum was injected directly into the muscle of nonsensitized animals. In the latter, the injection of horse serum caused a mild exudative reaction which was followed by a slight proliferation of connective tissue. The nerve fibrils within the muscle revealed no alteration at first, but after forty-eight hours they were swollen and degenerated. No changes were observed in the tibial and sciatic nerves. In the sensitized animals, the intramuscular injection of serum caused an immediate and severe exudative inflammatory reaction, which was followed by proliferation of connective tissue and formation of granulation tissue in the muscle. The intrinsic nerve fibrils of the muscle were swollen and degenerated within an hour after the injection. The perineurium of nerve branches within the muscle participated in the process of edema, leukocytic infiltration and fibrinoid swelling of the small arterioles. Swelling and wallerian degeneration of the nerve fibers of the tibial nerve were observed. Participation of nerve fibrils in the allergic inflammatory reaction may be the cause of the loss of sensation that has been noted in allergic reactions of the skin and may be a factor in the development and course of allergic inflammation.

O. T. SCHULTZ.

Pathologic Anatomy

VASCULAR COMMUNICATIONS BETWEEN THE CORONARY ARTERIES AND THE CHAMBERS OF THE HEART. J. T. WEARN and Others, Am. Heart J. **9**: 143, 1933.

By the employment of injection methods it has been possible to demonstrate vascular communications between the coronary arteries and the chambers of the heart. Serial sections and wax plate reconstructions of these communicating vessels revealed two types which have not been described previously. The first type are small branches of arteries or arterioles lying near the endocardium. They run a short course and empty directly into the lumen of the heart and for this reason they have been referred to as "arterioluminal" vessels. The second type arise as branches of arteries or arterioles and soon break up into sinusoids which lie between the muscle bundles and at times between the individual muscle fibers. These vessels have been referred to as "arteriosinusoidal" vessels, and the sinusoids have been designated as "myocardial sinusoids." The histologic structure of the "myocardial sinusoids" indicates that they play a rôle in the nourishment of the heart muscle.

AUTHORS' SUMMARY.

INTRACRANIAL HEMORRHAGE OF THE NEW-BORN. A. LEVINSON and O. SAPHIR, Am. J. Dis. Child. **45**:973, 1933.

In forty-five cases of intracranial hemorrhage in the new-born there was a striking lack of cellular reaction in the meninges. We believe that the small number of clinically evidenced complications of intracranial hemorrhage in children who survive can be explained by the absorption of the hematoma without organization and without the formation of a fibrous scar. Three of the instances of intracranial hemorrhage occurred in premature infants delivered by cesarean section, indicating that trauma was not the principal cause of the hemorrhages. Maternal toxemia seemed a possible contributory factor in the hemorrhages in these three infants. In our series there was no relationship between intracranial hemorrhage and atelectasis.

FROM THE AUTHORS' SUMMARY.

PATHOLOGIC CHANGES IN THE HEART IN AURICULAR FIBRILLATION. HENRY K. MOHLER and BAXTER L. CRAWFORD, Am. J. M. Sc. **187**:171, 1934.

The hearts of fifteen persons who had auricular fibrillation and of seven who did not have it, all of whom had had rheumatic fever and had lesions of the mitral valves, have been studied. The hearts of nine persons who had auricular fibrillation with arteriosclerosis as the etiologic factor were also studied; seven had sclerotic changes in the mitral valves while two apparently had normal valves. There were no pathologic changes common to all these cases of auricular fibrillation. Nothing in this investigation indicates that the type of pathologic lesion found at autopsy can of itself be responsible for the onset and continuation of auricular fibrillation. Etiologic factors apparently determine the type of pathologic changes to be found in the heart to a greater extent than does the presence or absence of fibrillation.

FROM AUTHORS' SUMMARY.

A HEMORRHAGIC ERUPTION OF THE MOUTH AND THROAT IN THE RHEUMATIC STATE. EDWARD HOLTZ and GEORGE FRIEDMAN, Am. J. M. Sc. **187**:359, 1934.

In patients with rheumatic heart disease an exanthem of hemorrhagic spots was observed in the mucous membranes of the mouth and throat. It was also noted in other diseases included in the concept of the rheumatic state and in relatively few patients in whom rheumatic infection was not apparent. It has been seen more frequently in rheumatic heart disease than in any other condition, and the seasonal peak of its frequency in this disease

coincides with that of acute upper respiratory infections and carditis. A lesion removed from the buccal mucosa during an exacerbation of acute carditis in a case of chronic rheumatic mitral and aortic endocarditis is described as a circumscribed area of hemorrhage in an edematous squamous layer of epithelium. There is increased vascularity of the epithelial and subepithelial layers. The changes in the blood vessels are: thickening of the media and intima, endothelial proliferation and in many vessels a shelflike protrusion of the hyperplastic intima into the lumen.

ESTHER C. MARTING.

FACTS ON DISEASE OF THE CORONARY ARTERIES, BASED ON A SURVEY OF 762 CASES. R. L. LEVY, H. G. BRUENN and D. KURTZ, Am. J. M. Sc. **187**: 376, 1934.

A statistical analysis was made of the postmortem and clinical records of 762 cases of disease of the coronary arteries observed at the Presbyterian Hospital [New York] during the period from 1910 to 1931. The facts apparent are to be regarded as applying to this material; no general conclusions are drawn. Arteriosclerosis was the most common lesion, being found in 97.2 per cent of the cases. Syphilitic aortitis, by inducing stenosis or occlusion of the coronary orifices, was responsible for impairing the coronary blood flow in 5.7 per cent. Syphilis did not predispose to coronary sclerosis; it was present no more frequently in patients with coronary disease than in those without this disease. In 2,877 consecutive autopsies, lesions of the coronary arteries were found in 25.9 per cent. This is a strikingly high figure. In half of the cases showing sclerosis in the coronaries, the lesions were "slight" or "moderate"; in many of these instances, no functional impairment of the cardiac circulation was induced by such lesions. The lesser degrees of sclerosis were observed predominantly in the younger age groups; the more marked lesions developed with advancing years. In this series of autopsies the incidence of coronary disease showed a slight but steady increase throughout a twenty-two year period; but the increase was not nearly so great in the proved cases as was indicated by the figures based on clinical diagnosis alone. Explanations of these facts are given. Disease of the coronary arteries increased at all ages, but the increase was particularly noteworthy between the age of 25 and 44. There was a predominance of males. The number of cases increased in both sexes. Occupation did not appear to play a significant part in determining those whose vessels were affected. The largest percentage of cases occurred among foremen and skilled workers. The clinical diagnosis of coronary disease is being made with greater accuracy as well as with increased frequency. Many cases are latent and probably cannot be recognized during life. Even in the presence of calcification or stenosis, the diagnosis was made clinically in but 16 per cent of the cases during the years 1920 to 1931. During this same period coronary thrombosis was correctly diagnosed in only 43 per cent of the cases. Arteriosclerotic heart disease was the most frequent primary cause of death. Cardiac insufficiency was the commonest terminal event. The increase in the incidence of disease of the coronary arteries is not to be regarded as a matter of concern. Rather should it be a source of satisfaction that, owing largely to effective control of infectious diseases, men may survive to an age when disorders incident to senescence lead to the termination of life.

AUTHORS' SUMMARY.

BENZOL POISONING WITH HYPERPLASIA OF THE BONE MARROW. D. H. ANDERSEN, Am. J. Path. **10**:101, 1934.

A case of benzene poisoning has been reported in which there was progressive diminution of the cellular elements of the blood, but in which the blood contained young cells and the bone marrow was extremely hyperplastic. Two similar instances have been collected from the literature, together with two of leukemia associated with exposure to benzene.

FROM THE AUTHOR'S SUMMARY.

CALCIFICATION OF THE SKIN AND SUBCUTANEOUS TISSUES. N. N. EPSTEIN and Others, Arch. Dermat. & Syph. **28**:510, 1933.

A woman, aged 56, had had firm nodules and plaques in the skin and subcutaneous tissues of the right side of the abdomen near the groin and in the right groin and thigh for twenty years. Many of the lesions became eroded and discharged a chalky material. Complete physical and laboratory examination revealed no other signs of abnormal calcification. The calcium and phosphorus of the blood were normal. Histologic section showed deposition of calcium in the collagenous fibers of the dermis and subdermis. The authors consider the underlying process to have been a disturbance of the collagenous material, probably of a physiochemical nature. One area suggested bony transformation.

S. W. BECKER.

HYPERTROPHIC STRIAE DISTENSAE. MICHAEL H. EBERT, Arch. Dermat. & Syph. **28**:825, 1933.

Three cases of striae cutis distensae appearing in young nonpregnant girls were studied. The early stage showed inflammatory changes with degeneration of the elastin. Ebert believes that in pregnancy striae result not only from an increase of mechanical tension in the skin but from degeneration of the elastic tissue due to some toxic agent probably produced by a disturbance of the endocrine system.

S. W. BECKER.

ELASTIC TISSUE IN FETAL SKIN. FRANCIS W. LYNCH, Arch. Dermat. & Syph. **29**:57, 1934.

Tissue was examined from thirty-five fetuses, varying in age from 2.6 to 8.9 months, by azocarmine, Van Gieson and Weigert elastic tissue stains. As early as the third month substances in connective tissue cells and in their processes in the walls of blood vessels, and at the boundary between the epidermis and the dermis stained with resorcinol fuchsin stain. Lynch does not regard this substance as elastin, but he found definite elastic fibers in the blood vessels of the dermis in the fifth month and in the dermis early in the sixth month.

S. W. BECKER.

ALEUKEMIC MYELOSIS. C. W. BALDRIDGE and W. M. FOWLER, Arch. Int. Med. **52**:852, 1933.

Ten cases are reported in which a common feature was myeloid hyperplasia. Two cases were ordinary instances of leukemic myelosis, except that in the course of each there developed an almost completely aleukemic period. In one case the aleukemic period was thought to be due to irradiation of the spleen; in the other, it was "spontaneous." In four cases in which the condition was thought to be diffuse hyperplasia of the myeloid tissue there were severe anemia, leukopenia, a few abnormal leukocytes, secondary hemorrhagic purpura, changes in the bones and extramedullary collections of myeloid cells. In two cases the hyperplasia was indistinguishable from ordinary multiple myeloma, except that the tumors were made up of myeloid cells instead of plasma cells. One case presented chemical changes sometimes seen in multiple myeloma of the plasma cell type. In the last two cases extramedullary myeloid tumors were present without definite evidence of disease of the bone marrow.

AUTHORS' SUMMARY.

INTRA-UTERINE RHEUMATIC HEART DISEASE. R. W. KISSANE and R. A. KOONS, Arch. Int. Med. **52**:905, 1933.

A child was born with active rheumatic fever and a cardiac lesion, whose mother had suffered from this disease throughout her pregnancy. These facts were affirmed by the husband and the attending physician, and at autopsy, nine

years later, the heart disease was demonstrated to be rheumatic with no evidence of congenital anomalies. Autopsy revealed the right side of the heart to be greatly dilated, and it had rotated in such a manner that the left auricle formed the right border of the heart. Therefore it is obvious that the intra-uterine transmission of rheumatic fever and heart disease is not only probable but possible.

AUTHORS' SUMMARY.

CORONARY THROMBOSIS WITH PERFORATION OF THE INFARCTED INTERVENTRICULAR SEPTUM. ROBERT V. SAGER, Arch. Int. Med. **53**:140, 1934.

The literature on perforation of the infarcted septum in coronary thrombosis is reviewed, and an additional case is reported. The postmortem findings have been those of infarction of the lower portion of the interventricular septum, usually due to a thrombotic occlusion of the coronary artery. In the majority of cases both the anterior and posterior descending arteries were involved.

EDWIN K. PROVOST.

A COMPARISON OF THE DEVELOPMENT OF THE SPECIFIC NODULE OF SILICOSIS AND OF TUBERCULOSIS. W. S. LEMON and W. H. FELDMAN, Arch. Int. Med. **53**:367, 1934.

In order to obtain material for a comparative study of the reactions provoked in the lung by particulate silica and by tubercle bacilli, intratracheal injections were given to two series of rabbits. The animals were killed at intervals of from four hours to four weeks, and the course and the character of the resultant cellular response were studied histologically. The results obtained appear to warrant the following conclusions: The character of the cellular response to the irritative influences of particulate silica and to tubercle bacilli is essentially the same; both irritants promote the formation of a characteristic tubercle. The properties of the provocative agent responsible for the production of the silicotic nodule preclude continuous progression. Thus this nodule contrasts markedly with that formed as a consequence of the injection of tubercle bacilli, which is usually of a progressive, destructive nature. The similarity of the structural units invoked in response to particles of silica and to tubercle bacilli is so striking as to make their identification impossible by ordinary morphologic criteria.

FROM AUTHORS' SUMMARY.

ARTERITIS OF THE TEMPORAL VESSELS: A PREVIOUSLY UNDESCRIBED FORM. BAYARD T. HORTON, THOMAS B. MAGATH and GEORGE E. BROWN, Arch. Int. Med. **53**: 400, 1934.

A woman, aged 55, and a man, aged 68, had fever, weakness, anorexia, loss of weight, anemia, mild leukocytosis and painful, tender areas over the scalp and along the temporal vessels. The symptoms had been present for from four to six weeks. Localized periarteritis and arteritis were present in each case. Relapses or complete remissions had occurred in both. The microscopic sections of the blood vessels removed for biopsy disclosed identical lesions. Peculiar circumscribed areas of what appeared to be granulation tissue were present in the adventitia and suggested granuloma; this was the most characteristic lesion present. The Gram stain revealed minute, filamentous, gram-positive material in these areas which could easily be interpreted as mycelium. In addition, an infiltration by round cells was present in the adventitia around the vasa vasorum and to a slight extent in the media. There was hemorrhage in the media in some regions. The intima in many places was markedly thickened; the basal portion appeared acellular, and there were superimposed cellular layers, which indicated that the intimal proliferation had taken place in different stages. In other areas the thickened intima was uniformly cellular. In some sections a small lumen was still present, whereas in

others the lumen had been completely occluded by either cellular or acellular thrombi. Both patients apparently recovered, although one died about two years later from heart failure and renal insufficiency. This condition may represent a new clinical syndrome the etiology of which is still obscure.

FROM AUTHORS' SUMMARY.

PROGRESSIVE NECROSIS OF THE SPINAL CORD. FREDERICK P. MOERSCH and JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **31**:504, 1934.

Moersch and Kernohan justly emphasize the necessity of differentiating myelitis, which is rare, from softening or what they choose to call progressive necrosis of the cord. In the latter condition the blood vessels show no inflammatory phenomena or other changes, such as thrombosis or embolism, that could be responsible for the softening. The cause of the latter, they believe, is most likely some unknown factor—a bacterial or other toxin. The cord tissue is disintegrated—the myelin and axons are broken up and transformed into lipoids. In some instances there is no glial reaction.

G. B. HASSIN.

HISTOLOGIC CHANGES IN THE BRAIN IN FATAL INJURY TO THE HEAD. CARL W. RAND and CYRIL B. COURVILLE, Arch. Neurol. & Psychiat. **31**:527, 1934.

The changes in the nervous system caused by fatal injuries to the head have been studied by Rand and Courville in thirty-nine patients. The period of survival was a few hours to three weeks, and in some cases in which hemorrhages were present it was several months. With the silver methods of Cajal and Bielschowsky it was possible to demonstrate changes in the central nervous fibers which were similar to those described by Cajal in experiments on animals: varicosities of the axons, corkscrew twistings, formation of loops, end-bulbs and many others. The end-bulbs, which were present in both the central and peripheral stumps of injured nerves, appeared as early as two hours after the injury and were quite typical "by four hours." They were short-lived in the peripheral segment of the injured nerves and lasted much longer in the central. Hemorrhages in the brain produced similar changes.

G. B. HASSIN.

CELLULAR INCLUSIONS IN CEREBRAL LESIONS OF EPIDEMIC ENCEPHALITIS: SECOND REPORT. JAMES R. DAWSON JR., Arch. Neurol. & Psychiat. **31**:685, 1934.

In two children, aged 5 and 16, with histories of a cerebral disturbance that clinically somewhat resembled epidemic (lethargic) encephalitis, Dawson found, among inflammatory and degenerative changes in the brain, intranuclear inclusions in the ganglion and glia cells. Only severely degenerated ganglion cells harbored the inclusions, which were round or oval, homogeneous or granular masses. They were single or multiple and entirely separate from the nucleoli. Inoculation of rabbits with emulsions of the brains of the two patients failed to produce encephalitis.

G. B. HASSIN.

MECKEL'S DIVERTICULUM CONTAINING ABERRANT PANCREAS. V. C. HUNT and H. T. S. BONESTEEL, Arch. Surg. **28**:425, 1934.

The literature contains reports of 186 cases of accessory or aberrant pancreas; in 178 cases the aberrant pancreas was found in the stomach, duodenum, jejunum or ileum. For the most part the aberrant pancreas existed as a nodule in the normal gastro-intestinal wall. In 33 cases, however, it was found in a diverticulum of the stomach, duodenum, jejunum or ileum. In only 13 of these cases was the diverticulum classed as Meckel's diverticulum. The case herein reported is the fourteenth recorded case of a true diverticulum containing pancreatic tissue.

FROM THE AUTHORS' SUMMARY.

MECKEL'S DIVERTICULUM WITH ADENOMA AND INTESTINAL BLEEDING. R. N. SCHULLINGER and A. P. STOUT, Arch. Surg. **28**:440, 1934.

Meckel's diverticulum with a pedunculated adenoma of gastric and duodenal glands at the tip was found in a boy of 16 who was taken with acute abdominal pain and intestinal bleeding. The exact source of the bleeding was not determined. In cryptic intestinal bleeding as well as in acute obscure abdominal attacks the possibility that Meckel's diverticulum may be involved should not be overlooked.

THE HYPOPHYSIS OF THE HUMAN CASTRATE. J. H. BIGGART, Bull. Johns Hopkins Hosp. **54**:157, 1934.

The hypophyses of four castrated human beings are described. The changes were: (1) a marked increase in basophils; (2) the appearance of large chromophobe cells with stages of transition between these and basophils; (3) a varying response on the part of the eosinophils; (4) vacuolation and colloid formation in the basophils. The possible physiologic significance of these changes is discussed.

FROM THE AUTHOR'S SUMMARY.

THE LUNGS IN EXFOLIATIVE DERMATITIS. A. K. POOLE and R. T. WEHGER, J. A. M. A. **102**:745, 1934.

Of seventeen cases of exfoliative dermatitis with observations at autopsy reports of which have been collected from the literature, fourteen showed pulmonary pathologic changes. All four of our cases showed epithelial exfoliation of the respiratory tract and no evidence of pneumonia. A similar process may occur in the kidneys. It seems that an important contributing cause of death in exfoliative dermatitis is not pneumonia but obstruction of the air passages due to exfoliation of the epithelium.

FROM THE AUTHORS' SUMMARY.

STRUCTURAL CHANGES IN EXPERIMENTAL BLACK TONGUE. R. D. LILLIE, Nat. Inst. Health Bull. 162, 1933, p. 13.

Erythematous and ulcerative lesions of the oral mucosa with early epithelial and papillary edema, followed by exfoliation, superficial necrosis and pseudomembranous inflammation, and often accompanied by degenerative changes in the regional nerves, were quite regularly seen in dogs dying in attacks of black tongue. Diffuse and focal congestion of the gastro-intestinal mucosa, with or without oozing of blood, hemorrhage and tarry contents were noted, but as similar changes may be observed in dogs killed by gas or chloroform, little significance is to be attached to these grossly striking findings. Distorted cystic glands filled with mucus or mucopus were sometimes seen in black tongue. The lungs presented no lesions specifically attributed to black tongue. Bronchopneumonia of similar character has been seen in black tongue and yellow liver is not significantly different frequency, as well as in other dogs. Granular degeneration of the cardiac muscle fibers was seen. Moderate passive congestion and relatively little fatty infiltration were seen in the liver in black tongue. The spleen more often than otherwise was anemic and fibrotic and contained atrophic follicles. Fatty infiltration of the coarse limbs of Henle's loops in the kidney, often seen in normal dogs, was present in only about half the animals dying of black tongue. Albuminous degeneration of the epithelium of the convoluted tubules was quite common, fatty changes being rather infrequent in black tongue. Glomerular epithelial degeneration and intracapsular exudation were noted rather infrequently. The suprarenal glands appeared normal or not significantly altered. Usually the pancreas was normal, the exceptions being regarded as accidental complications rather than as significant for the condition under study. Injection of the meninges was seen in about half the brains examined. Tigrolysis in the ganglions of the brain stem was more or less frequent and extensive, and nerve cell atrophy and pericellular vacuolation in the cortex and basal ganglions were often seen.

FROM THE AUTHOR'S SUMMARY.

FATTY INFILTRATION OF THE LIVER ("YELLOW LIVER") ASSOCIATED WITH DEFICIENT DIETS. R. D. LILLIE and W. H. SEBRELL, Nat. Inst. Health Bull. 162, 1933, pp. 23 and 37.

PART 1 (Sebrell).—An experimental condition in dogs characterized, at least terminally, by coma and subnormal temperature is described. Death usually occurred within two days from the first observance of symptoms, and extensive fatty changes in the liver were found at autopsy. This condition is shown to be associated with diets deficient in or perhaps containing a marginal quantity of the black tongue preventive factor (vitamin G). Since the condition occurs simultaneously with, after or independent of the ordinary clinical symptoms of black tongue, and since the pathology is entirely different from that of acute black tongue, it appears that the condition is either distinct from black tongue (and therefore due to a deficiency in a hitherto unrecognized factor which is closely associated with the black tongue preventive factor [vitamin G]) or is a hitherto unrecognized manifestation of the black tongue syndrome. The condition is prevented by the addition of dried or autoclaved yeast to the diet. Further studies are necessary to decide whether yellow liver is clinically and etiologically distinct from the black tongue syndrome.

PART 2 (Lillie and Sebrell).—Lesions of the buccal mucosa were absent except as a result of concomitant black tongue. Diffuse and focal congestion of the gastric and intestinal mucosae, with or without oozing of blood, hemorrhage and tarry intestinal contents were noted but did not appear especially significant, as grossly similar findings may be observed in normal dogs killed with carbon monoxide or chloroform. Distorted cystic intestinal glands filled with mucus or mucopus were occasionally observed, but may be attributed to previous attacks of black tongue. The most striking finding was the firm, friable, greasy, yellow liver which microscopically was diffusely infiltrated with fat. Fatty infiltration of the epithelium of the coarse limbs of Henle's loops, often seen in normal dogs, was practically constant. Albuminous and fatty degeneration of the convoluted tubules was quite common. Glomerular epithelial degeneration and intracapsular exudation were infrequent. The suprarenal glands showed rather marked medullary and inner cortical congestion in a few animals, but more often appeared normal or not significantly altered. The pancreas was usually normal, the exceptions being regarded as accidental complications. Injection of the meninges was seen in about half the animals. Severe, diffuse, quite general fatty degeneration of the white substance of the brain and cord was shown by the Marchi method in two of eight animals only. Tigrolysis in the ganglions of the brain stem and nerve cell atrophy and pericellular edema in the basal ganglions and cortex were observed.

FROM THE AUTHORS' SUMMARIES.

HISTOPATHOLOGY OF ANAL CRYPTS. C. C. TUCKER and C. A. HELLWIG, Surg., Gynec. & Obst. **58**:145, 1934.

Histologic study of hemorrhoids and infected anal crypts revealed preformed anal ducts which opened into the crypts of Morgagni. These ducts are regarded as remains of complex glandular organs as found in the lower orders of mammals. The narrow tubular structures afford a ready path for infective organisms, communicating as they do with the bowel lumen. So called cryptitis, anal fistula and periproctitic abscess have their origin in these anal ducts. The length and direction of these structures determine the extension of an anal infection. The existence of preformed epithelial tubules extending from the anal canal into the surrounding tissue explains the frequency of anal infection and why so-called cryptitis and anal fistula do not heal, as a rule, when the method of treatment is conservative.

FROM THE AUTHORS' SUMMARY (W. C. HUNTER).

CHRONIC FOLLICULAR GASTRITIS. C. R. K. JOHNSTON, Surg., Gynec. & Obst. **58**:614, 1934.

The conclusion seems justifiable that chronic gastritis is almost constantly associated with peptic ulcer, gastric ulcer, gastric cancer or stomal ulcer. In the

present series, seven cases showed microscopically a chronic inflammatory change in the absence of ulceration. In four of these the condition was diagnosed as chronic follicular gastritis and had been considered as duodenal ulcer in three cases and carcinoma of the pylorus in the fourth. Of the three cases of chronic gastritis in which no ulcer was found, one had been diagnosed by x-ray picture as a case of gastric ulcer, while the two remaining cases had a more or less obvious cause for the gastritis. In view of these findings I believe that one must accept that chronic follicular gastritis may exist as a definite entity in the absence of ulceration. This belief is shared by a number of writers (Faber, Fitzgerald and others). The cause of the gastritis and its exact relationship to peptic ulcer, that is, whether it is primary or merely secondary to the ulceration, has not yet been definitely established. I am inclined to view the gastritis as primary, and believe that therein lies a fertile field for seeking the origin of chronic peptic ulcer.

FROM THE AUTHOR'S SUMMARY (W. C. HUNTER).

THE THYROID GLAND IN MENTAL DEFICIENCY. J. L. NEWMAN, J. Ment. Sc. **79**: 464, 1933.

The variations in structure are marked. It is not possible to find any feature which would distinguish primary from secondary amentia, nor were the appearances of the thyroid gland in any of the subtypes of these groups consistent save in mongolian idiots, in whom a diminution of thyroid function was apparent. In a series of children's thyroid glands the epithelial cells grew syncytially and infiltrated the colloid; the process may obscure the original alveolar structure. Another feature of the gland of childhood is the so-called "cell masses," which, however, are of no more significance here than in the adult. Some increase may be found in the fibrous stroma of the thyroid gland of the quite young child in whom there is no obvious excessive functional demand on the gland. The colloid may vary in its appearance and staining reactions, being hyaline, granular or apparently mucoid and either acid or alkaline in its staining affinities. The state of nutrition seems to have no connection with the histologic appearance of the gland. Fever, on the other hand, at first leads to absorption of colloid and increased activity on the part of the epithelium. But if the fever is continued, overcompensation is the results and the gland then reverts to a condition of colloid storage with diminished cellular activity.

WILLIAM FREEMAN.

ANEURYSM OF THE PULMONARY ARTERY. R. D'AUNOY and E. VON HAAM, J. Path. & Bact. **38**:39, 1934.

Two cases of aneurysm of the pulmonary artery with Botallo's duct patent are reported, with a complete review of the cases of aneurysm of the pulmonary artery reported to date. In the first case that we report, a syphiliic involvement of the pulmonary artery, together with increased blood pressure caused by patent Botal's duct, may be considered the etiologic factor. In our second case, a congenital defect, patent Botallo's duct, was complicated by septic endarteritis and endocarditis. Both cases demonstrate the importance of two factors in the etiology of aneurysm—damage to the wall of the vessels and increased blood pressure.

AUTHORS' SUMMARY.

REGENERATION OF SKELETAL MUSCLE IN YOUNG RABBITS. W. G. MILLAR, J. Path. & Bact. **38**:145, 1934.

The skeletal muscle of young rabbits regenerates readily after trauma. Regeneration appears to take place from the damaged ends of otherwise intact muscle fibers and not from individualized cells nor to any effective degree from muscle giant cells. New myofibrils are laid down in the cytoplasm of the muscle bud, probably in continuity with existing myofibrils. Cross-striation appears rather late in the process, the Krause membranes appearing first, the Q disks later.

The Q substance only relatively slowly develops its specific Kull-staining properties. The laying down of myofibrils is associated with a striking and apparently hitherto undescribed change in the nucleus. FROM THE AUTHORS' SUMMARY.

Pathologic Chemistry and Physics

BLOOD GLUTATHIONE IN TUBERCULOSIS. RUSSELL N. LOOMIS AND EMIL BOGEN, Am. Rev. Tuberc. **30**:505, 1934.

The active sulphydryl compound, glutathione, was discovered in yeast cells and animal tissues more than a decade ago, but only recently has its chemical composition been established. It is widespread throughout the body. The slightly lowered carbon dioxide-combining power of the blood in pulmonary tuberculosis, the lowered vital capacity of the lungs and the increased lactic acid content of the blood are consistent with the idea of suboxidation in this disease, but there has been, as yet, no direct evidence of the existence of such a factor. Tuberculous tissues have been reported to be deficient in reduced glutathione, but the few analyses available fail to show any consistent change in the glutathione content of the blood. Both reduced and total glutathione were determined by the method of Woodward and Fry *(J. Biol. Chem.* **97**:465, 1932). Although overlapping of the series tested was found, the increase in the total and in the reduced glutathione, and particularly the lessening in the difference between them, appear quite definite, and suggest an actual condition of suboxidation in tuberculosis. The differences appeared somewhat more marked among guinea-pigs in which the disease had progressed for a longer time. Rabbits showed similar differences. Forty-eight patients with advanced pulmonary tuberculosis also showed an increase in the reduced glutathione and a lessening in the difference caused by zinc (dust) treatment of the filtrate. H. J. CORPER.

THE CHOLESTEROL AND VITAMIN A CONTENT OF THE LIVER IN MAN. G. L. MULLER AND M. M. SUZMAN, Arch. Int. Med. **54**:405, 1934.

The cholesterol content of the liver at autopsy in 106 cases ranged from 0.098 to 1.003 Gm. per hundred grams, with an average of 0.301 Gm. Statistically no relation could be established between the cholesterol and the vitamin A content of the liver or the sex or the age of the patient. The cholesterol content of the liver tended to be lower than the average in patients who died of infections, and highest in those who died of arterial hypertensive disease, with that of patients who had malignant tumors as a cause of death occupying an intermediary position. FROM THE AUTHORS' SUMMARY.

URINARY CALCULI ASSOCIATED WITH PARATHYROID DISEASE. F. H. COLBY, Surg., Gynec. & Obst. **59**:210, 1934.

In eight of thirteen patients operated on for parathyroid tumors there were calculi in some part of the urinary tract. In six instances the calculi were renal in location. In three patients the bony changes typical of parathyroid disease were not prominent and were quite overshadowed by symptoms referable to the urinary system. The true condition of these patients was recognized in the high serum calcium and the low serum phosphorus. W. C. HUNTER.

MICROLITHS OF BILE AND GALLSTONES. B. OHSE, Virchows Arch. f. path. Anat. **292**:442, 1934.

Ohse insists that the term "microlith" should be limited to the bodies originally so named by Meckel in 1856 in his treatise on microgeology. They are spherical or ovoid, from 10 to 200 microns in diameter, possessed of a central nucleus, and radially or concentrically striated. The concentric layers may be green or yellow. The microliths are formed in the biliary passages during life. They are not

artefacts and cannot be produced artifically in gallbladder bile. They may occur within gallstones, but whether as elements incorporated into the stone or as a center of stone formation cannot be determined. Many calculi do not contain them, and hence they cannot be considered essential to stone formation. There is no evidence that inflammation of the biliary passages is a necessary factor in the formation of microliths. They probably result from the diffusion of ions into a protein gel. The microliths of uric acid infarcts are analogous to those of bile.

O. T. Schultz.

The Phosphatide Content of the Brain in Niemann-Pick Disease and in Infantile Amaurotic Idiocy. E. Epstein, Virchows Arch. f. path. Anat. **293**:135, 1934.

Cases in which an enlargement of the spleen and the hepatic changes of Niemann-Pick disease are associated with the retinal changes of Tay-Sachs disease have led to controversy as to whether they are examples of a combination of the two diseases, and whether phosphatide lipoidosis and infantile amaurotic idiocy are two distinct diseases or two different types or stages of the same disease. Epstein's previous chemical work, which has been confirmed by others, showed that the characteristic feature of Niemann-Pick disease is the storage of phosphatide lipoids in the reticulo-endothelial system. The brain contained twice as much phosphorus in the form of ether-soluble and alcohol-soluble lipoids as the brain of a normal child. Epstein now reports the results of his chemical investigation of three brains from children with amaurotic idiocy. The brains were fixed in solution of formaldehyde. As a control, the similarly fixed brain of a normal child of the same age was examined. Lipoid phosphorus was not increased, but was definitely decreased as compared with the normal. Epstein concludes that the two diseases in question are distinct, and that the retinal lesion of phosphatide lipoidosis is not the same as that of amaurotic idiocy. In a second part of the paper Epstein and K. Lorenz discuss the changes that occur in the phosphatides when the brain is preserved in solution of formaldehyde. A progressive decrease in phosphatides occurs, owing to their gradual transformation into water-soluble compounds. A true estimate of the phosphatide lipoids is not possible unless the brain has been kept in the original solution of formaldehyde, which must also be chemically examined. They believe, furthermore, that the chemical changes described affect the conclusions to be drawn from microchemical stains for lipoids if the material has been long in solution of formaldehyde.

O. T. Schultz.

The Rôle of the Lipoids of the Serum. St. Went and A. von Kúthy, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:392, 1934.

The proteins of the serum were freed from the lipoids with alcohol and ether. Watery solutions of the lipoid-free proteins were precipitated with sodium sulphate. The usual pseudoglobulin fractions were obtained while the precipitate of euglobulin was considerably more abundant than when the native serum was precipitated. On the other hand, the euglobulin fraction of the lipoid-free solutions of the serum proteins was considerably smaller than the corresponding native euglobulins. This change may have been due to an increase of hydrophobia brought about by the partial denaturation. When watery solutions of lipoids were added to the solutions of proteins from which lipoids had been previously removed, the original physical chemical properties were not restored, indicating that the splitting of the lipoid protein complex is irreversible.

I. Davidsohn.

Microbiology and Parasitology

Experimental Epizootic Fox Encephalitis in Dogs. R. G. Green and J. E. Shillinger, Am. J. Hyg. **19**:362, 1934.

Dogs may be experimentally infected with the virus of fox encephalitis. We have found an irregularity in our attempts to transmit the disease that appears best

explained on a basis of familial natural immunity. The fatal infection usually runs a short, violent course of less than a week in a manner similar to that of the infection in foxes. The lacrimal and nasal secretions of the dog tend to become purulent. The nervous symptoms are largely concerned with a state of excitement, often describable as a running fit. There are cellular infiltration in the central nervous system and focal necrosis of the liver. Specific intranuclear inclusions are found in the vascular endothelium, meningeal cells, reticulo-endothelium, hepatic cells and occasionally in the cortical cells of the suprarenal glands. [Green and others report the results of their work on the virus of fox encephalitis in the *American Journal of Hygiene* (**19**:343, 1934)].

FROM THE AUTHORS' SUMMARY.

BACTERIUM TULARENSE IN ROCKY MOUNTAIN WOOD TICK. G. E. DAVIS, C. B. PHILIP and R. R. PARKER, Am. J. Hyg. **19**:449, 1934.

Three strains of Bact. tularense of low virulence for rabbits and guinea-pigs have been isolated from Dermacentor Andersoni. This is in marked contrast to numerous other isolations from this tick. The occurrence in nature of strains of Bact. tularense of different degrees of virulence is indicated. It is believed that in making tests to determine the relative virulence of strains the use of both guinea-pigs and domestic rabbits will prove advantageous.

FROM THE AUTHORS' CONCLUSIONS.

STUDY OF A GROUP OF STREPTOCOCCI. R. L. THOMPSON and E. MEGRAIL, Am. J. Hyg. **19**:457, 1934.

In a group of 120 strains of streptococci, chiefly of human origin, a high correspondence was found between plate hemolysis, test tube hemolysis and the limiting hydrogen ion concentration. As a rule, the same strains were inhibited by sodium chloride, sodium ricinoleate, ox bile and certain dyes. Growth of most of the beta and about half of the nonbeta strains was uniformly inhibited by these agents. Stains which were resistant to the bacteriostatic reagents possessed low iso-electric points; those which were nonresistant had high iso-electric points. All strains virulent for white mice produced beta hemolysis. Likewise, of the strains tested, all cultures found to be toxigenic were of the beta type. Individually or collectively, these tests failed to separate this group of streptococci into smaller groups of significant meaning.

FROM THE AUTHORS' SUMMARY.

REGRESSIVE LESIONS OF PRIMARY TUBERCULOUS INFECTION. HENRY C. SWEANY, Am. Rev. Tuberc. **27**:559, 1933.

Sweany studied the regression of the primary tubercle in 188 lungs removed at necropsy, roentgenographed and sectioned. The incidence and location of the lesions were found in keeping with the ideas of Küss, Ghon and others, but there was a higher incidence of what appeared to be multiple primary residues. This was attributed to the use of a more certain method of localization. Of 88 specimens of characteristic primary lesions, 76 were in the parenchyma and 65 in the lymphatics; 23 were located only in the parenchyma and 11 only in the lymph nodes. Bone was found in 22 of 84 calcified parenchymal lesions and in 23 of 97 lymph nodes, revealing practically no difference in bone formation between the local and the lymphatic lesion and an incidence of 25.1 per cent of all without the usual lymph node exaggeration. The mechanisms of calcification, ossification and resorption are described. The question arose as to the liberation of tubercle bacilli as a result of the resorption of the walls of the primary lesion, because walls were entirely gone in more relatively young persons, while bacilli were living in most large primary lesions in people under 25 years of age. Approximately half of the calcified parenchymal lesions may be seen in antemortem roentgenograms, for, of 98 showing in the postmortem pictures, only 48 could

be seen in the antemortem films. Ten lungs contained very small primary lesions and 30 none. Many of these two groups showed a modified type of primary lesion, indicating that there had been only a partial sensitizing effect from the first infection. Six appeared to be primary lesions in adults. H. J. CORPER.

SKIN LESIONS OF TUBERCULIN REACTING CATTLE. L. L. DAINES and H. AUSTIN, Am. Rev. Tuberc. **27**:600, 1933.

Careful microscopic search of smears from skin lesions of cattle reacting to tuberculin reveals in practically all lesions acid-fast and usually also nonacid-fast organisms of different shapes and sizes. On a modified moist Petroff medium with a small amount of carbon dioxide, cultures are obtained regularly from these lesions which either are acid-fast from the beginning or acquire acid-fastness on certain mediums. The cultures consist of pleomorphic, coccoid, diplococcoid, diphtheroid or solid rod-shaped organisms believed to be different stages of a pleomorphic organism, probably causing the lesions. Fairly characteristic skin lesions are produced by injecting acid-fast strains of these organisms into rats, white mice and guinea-pigs, while in cows typical lesions result. Tuberculin tests in guinea-pigs yield mostly positive reactions, while in cows the reactions are not constant, varying from negative to suspicious. Internal lesions in rats, white mice, guinea-pigs and cows resemble more nearly pseudotuberculosis of sheep produced by the Preisz-Nocard bacillus. The organisms have been consistently recovered in cultures from experimental lesions. Chickens fail to respond to the injection or the feeding of the organisms. The identification of the organisms has not been made, but they are not tubercle bacilli and possibly are an undescribed species.

H. J. CORPER.

THE EFFECT OF VIOSTEROL (VITAMIN D) AND TUBERCULIN ON THE HEALING OF TUBERCULOUS LESIONS IN GUINEA-PIGS. EUGENE C. DE SAVITSCH and Others, Am. Rev. Tuberc. **28**:699, 1933.

The use of a combination of viosterol and tuberculin in the treatment of moderately advanced tuberculosis in guinea-pigs gives definitely beneficial results as judged by longevity, degree of tuberculous involvement and amount of fibrosis. The optimal effect of the treatment is apparently obtained when the viosterol and tuberculin are given simultaneously rather than when one precedes the other by forty-eight hours. The average life span of animals receiving simultaneous treatment with viosterol and tuberculin is markedly increased as compared with that of the controls or of the tuberculous animals treated with either viosterol alone or tuberculin alone. The average degree of tuberculous involvement in animals receiving simultaneous treatment with viosterol and tuberculin and in those treated with viosterol followed in forty-eight hours by tuberculin is less than that of the controls or of the animals receiving tuberculin followed in forty-eight hours by viosteral. The average amount of fibrosis in animals receiving the combined treatment is definitely greater than that of the controls. H. J. CORPER.

TUBERCLE BACILLI IN THE BLOOD OF RABBITS FOLLOWING SUBCUTANEOUS AND INTRAPERITONEAL INOCULATION. LUCY MISHULOW and WILLIAM H. PARK, Am. Rev. Tuberc. **28**:875, 1933.

In a previous communication (*J. Prev. Med.* **6**:95, 1932) Mishulow and Park stated that when rabbits were inoculated intravenously with a culture of human tubercle bacilli the bacilli were present in the blood during the entire course of the infection. In the present study they tried to determine whether a bacteremia will also occur in rabbits that are infected by the subcutaneous or by the intraperitoneal route. They used bovine tubercle bacilli, and two rabibts were inoculated subcutaneously and two intraperitoneally. Cultures of the blood were made on Bordet-Gengou medium, and guinea-pigs were inoculated. The results obtained

showed that there was no demonstrable invasion of the blood stream in the rabbits inoculated with tubercle bacilli intraperitoneally and that there was such invasion in only one of the two rabbits inoculated subcutaneously. H. J. CORPER.

SILICOSIS AND ITS RELATIONSHIP TO TUBERCULOSIS. LEROY U. GARDNER, Am. Rev. Tuberc. **29**:1, 1934.

Silicosis is due to silica dust. It is of particular interest to the phthisiologist because it predisposes to infection with the tubercle bacillus. In this respect it differs from most other known types of industrial pneumonoconiosis. The diagnosis of silicosis is established by a history of exposure to silica dust in occupation, by a roentgenologic examination of the chest and to a lesser extent by physical examination. There is a decided tendency at first for pulmonary units situated beneath the pleura to be more heavily involved than those in the deeper portions of the lung. The formation of lymphoid nodules compresses the lumens of lymph vessels and impedes subsequently inhaled particles, with resultant fibrosis of perilymphatic distribution. Accompanying this change linear markings in the lungs are accentuated. Then follow peripheral nodules and obscuring of the linear markings. At least 75 per cent of the persons in whom silicosis develops die of tuberculosis, which may make its appearance at any stage of the disease. It becomes more frequent in the more advanced stages of silicosis. The characteristic lesion of silicosis is modified by the presence of an active tuberculous focus. The nodules become more abundant and closely packed together. Minute foci of caseation may or may not be detectable; cavity formation is a late manifestation. Animal experiments verify the accelerating influence of silica on tuberculosis. H. J. CORPER.

A TUBERCULOSIS SURVEY OF TWO THOUSAND FOOD HANDLERS IN NEW YORK CITY. D. C. MARTIN, H. T. PESSAR and J. A. GOLDBERG, Am. Rev. Tuberc. **29**:182, 1934.

Active tuberculous pulmonary lesions were found in approximately 2 per cent of apparently healthy food-handlers in New York City. With a food-handling population of more than 325,000 persons, this percentage represents the existence of not less than 6,500 cases of unknown and therefore uncontrolled active pulmonary tuberculosis. In addition, there is evidence of many thousands of cases of arrested tuberculosis, latent childhood tuberculosis and pleurisy among food-handlers. H. J. CORPER.

EXPERIMENTAL YAWS. T. B. TURNER and A. M. CHESNEY, Bull. Johns Hopkins Hosp. **54**:174, 1934.

The experimental disease produced in rabbits by eight strains of Treponema pertenue isolated in Haiti was compared with that produced by (1) a strain of Spirochaeta pallida isolated in Haiti and by (2) several strains of S. pallida isolated in the temperate zone. No differences were noted in the experimental infection in the rabbits inoculated with the eight strains of yaws virus. The disease picture produced by the yaws virus presented striking and for the most part constant differences from that produced by the Haitian strain of syphilis. The latter gave rise to an experimental disease which was similar in every way to that produced by the several strains of S. pallida isolated in the temperate zone. The bearing of these observations on the identity of syphilis and yaws is discussed.

FROM THE AUTHORS' SUMMARY AND CONCLUSIONS.

PNEUMOCOCCUS VARIATION. M. D. EATON, J. Bact. **27**:271, 1934.

Methods are described for the isolation from human sources and the artificial production of stable strains of Pneumococcus which undergo rapid lysis or fail to grow under the ordinary conditions at 37 C. Strains showing such character-

istics have been termed phantom colony variants or P-C variants. The effects of cultivation at 25 C., carbon dioxide, p_H and oxygen tension on the growth and lysis of P-C variants are described. The P-C variant strains are compared with normal forms as regards growth requirements, virulence and antigenic composition. Evidence is adduced that the P-C variation is a change independent of the ordinary smooth-to-rough variation. Methods are described for causing reversion of the phantom colony variants to normal-growing smooth forms by cultivation in alkaline mediums and under certain other conditions. The direct isolation of the phantom colony variants from infected human beings indicates further study of their possible rôle in disease.

FROM THE AUTHOR'S SUMMARY.

SWINE INFLUENZA. R. E. SHOPE, J. Exper. Med. **59**:201, 1934.

A strain of swine influenza has been observed to change from a condition of full contagiousness, in which both Haemophilus influenzae-suis and the swine influenza virus were transferred by pen contact, to one of only partial contagiousness, in which the virus alone was transferred, resulting in the mild filtrate disease instead of the swine influenza of animals infected by contact. Swine that had been experimentally converted into carriers of H. influenzae-suis contracted swine influenza following contact with animals infected with the altered strain of the disease. Experiments in which the etiologic components of a freshly obtained and fully contagious strain of swine influenza were substituted for the corresponding components of the altered strain of the disease revealed the fact that the change in the contagious character of the latter was due to an alteration in the bacterial component of the etiologic complex, and that the virus component was in no way responsible.

FROM AUTHOR'S SUMMARY.

SPECIFIC INHIBITION OF BACTERIOPHAGE ACTION BY BACTERIAL EXTRACTS. P. LEVINE and A. W. FRISCH, J. Exper. Med. **59**:213, 1934.

Experiments are presented demonstrating specific inhibition of bacteriophage by soluble products of bacteria. The inhibition proceeds more rapidly at 37 C. than at icebox temperature. The specificity of the reaction in the instances studied is probably connected with the presence of specific soluble carbohydrates. A reaction is available for the study of the chemistry of bacillary antigens in terms of bacteriophage.

FROM THE AUTHORS' SUMMARY.

SINGLE CELL INOCULATIONS WITH TREPONEMA PALLIDUM. C. S. THOMAS and H. J. MORGAN, J. Exper. Med. **59**:297, 1934.

The injection of one or several of the spirochetes of syphilis into the testicle of the rabbit does not induce syphilitic infection. A negative tissue transfer experiment does not preclude the presence of Spirochaeta pallida in the inoculum nor does it indicate the absence of syphilis in the source animal.

FROM THE AUTHORS' CONCLUSIONS.

A FATAL LABORATORY INFECTION OF RIFT VALLEY FEVER. F. F. SCHWENTKER and T. M. RIVERS, J. Exper. Med. **59**:305, 1934.

A case of Rift Valley fever following an accidental laboratory infection and believed to be the first instance of the disease in the Western Hemisphere is reported. Although the course was otherwise quite typical, it was complicated by thrombophlebitis—a condition not previously described in association with this disease in man. Death was caused by a pulmonary embolus.

FROM THE AUTHORS' SUMMARY.

BACTERIAL GROWTH AND MULTIPLICATION AS DISCLOSED BY MICRO MOTION PICTURES. R. W. C. WYCKOFF, J. Exper. Med. **59**:381, 1934.

Using a micromotion picture technic for making records, studies have been made of the growth of a number of bacteria, covering several thousand hours of observation. On the basis of these experiments a discussion is offered of bacterial division and its influence on gross colony appearance, of different kinds of pleomorphism that have been observed, and of the nature of the internal structure that is seen in some bacteria. Several of the micro-organisms chosen for examination have been thought to give evidence of life cycle phenomena. The present pictures, however, contain no evidence of a bacterial cycle in the commonly accepted meaning of the term.

FROM THE AUTHOR'S SUMMARY.

THE LOCALIZATION AND FATE OF BACTERIA IN THE TISSUES. F. L. SULLIVAN, E. F. NECKERMANN and P. R. CANNON, J. Immunol. **26**:49, 1934.

Living staphylococci and paratyphoid bacilli injected intravenously into rabbits are quickly removed from the circulating blood and are localized particularly in the liver and spleen, where they are ingested and destroyed by phagocytes. The lungs, bone marrow and omentum remove distinctly fewer numbers, and such organs as the kidneys, suprarenal glands, striated muscle, brain, testes and thyroid gland remove negligible numbers under comparable conditions. In other words, the primary localization occurs principally in the two organs containing many macrophages and a sinusoidal type of blood flow, whereas practically no localization occurs in organs poorly supplied with macrophages and having a rapid flow through vessels lined with ordinary endothelium. Active immunization does not significantly affect the comparative degrees of localization, although it leads to a more energetic removal of the bacteria from the blood stream by the liver and spleen. Bacteria are concentrated more quickly in the liver and spleen of the immune than of the normal animal but are also killed more rapidly within these organs. Comparatively few living bacteria of these types are eliminated by the bile. Active intravenous immunization leads to a stimulation of mesenchymal tissues, particularly in the liver and spleen, with a resulting elevation of the functional state of the system of macrophages.

FROM AUTHORS' SUMMARY AND CONCLUSIONS.

DIFFERENTIATION OF VARIOUS STRAINS OF MONILIA BY CULTURAL METHODS. M. WACHOWIAK and Others, J. Infect. Dis. **54**:35, 1934.

In view of the irregularities noted in the action of ninety-two strains of Monilia on various types of mediums, and especially on carbohydrate mediums, it does not appear justifiable to use such methods for the differentiation of species within this genus. The appearance of the growth of Monilia on solid mediums, the development of top or bottom growth in fluid mediums, the morphology of the stained organisms and the development of outgrowths or the types of outgrowths from colonies on plates do not offer satisfactory methods for the differentiation of species within this genus.

FROM THE AUTHORS' CONCLUSIONS.

ISOLATION OF BRUCELLA FROM HEALTHY SWINE. W. H. FELDMAN and C. OLSON JR., J. Infect. Dis. **54**:45, 1934.

Blood was obtained before slaughter from a group of 102 head of swine ranging in age from 7 to 12 months. Serum from this blood was used to conduct agglutination tests, using Brucella abortus as antigen. The blood serum of two of the animals showed definitely positive reactions, and these animals were subjected to careful postmortem examination. By inoculation of guinea-pigs an organism of the Brucella group was obtained from each of the animals whose serum had reacted positively in the agglutination tests. The organism was obtained from lymph nodes of the head and anterior cervical region and from an abscess of the

spermatic cord of one of the animals. In another animal the infective organism was secured from the spleen. Neither the lymph nodes nor the spleen revealed morbid changes. These observations indicate that bacteria of the Brucella group may exist in the tissues of apparently normal swine without giving rise to discernible symptoms of disease.

From the Authors' Summary and Conclusions.

Cataphoretic Time and Velocity of Streptococci and Pneumococci. E. C. Rosenow, J. Infect. Dis. **54**:91, 1934.

Streptococci and pneumococci isolated in studies of the common cold, influenza, simple bronchopneumonia, influenzal bronchopneumonia and lobar pneumonia have distinctive distribution curves of cataphoretic time and velocity on isolation. The serum during and following attacks of the common cold and of influenza contains specific antibodies (cataphoretic slowing power) for the streptococci of these diseases. The changes noted in the cataphoretic time and velocity of the streptococci during the rise and fall of epidemic waves of these diseases appear to be not merely coincidental but expressive of determinative properties. The etiologic importance of streptococci and pneumococci in these diseases is emphasized.

From the Author's Conclusions.

Proteolytic and Deaminizing Enzymes of Clostridium Sporogenes and Clostridium Histolyticum. Otto A. Bessey and C. G. King, J. Infect. Dis. **54**:123, 1934.

The proteolytic activity of filtrates from, or suspensions of, Cl. histolyticum is much greater than that found for Cl. sporogenes, but the general characteristics of the proteases are alike, showing an optimum p_H of 7.5 and the predominant formation of polypeptides. The deaminizing enzymes associated with Cl. histolyticum are much less active than those associated with Cl. sporogenes, this being true in greatest degree when tyrosine alone is supplied as a substrate. The enzymes of both organisms show a marked specificity in their deaminizing action on amino-acids, cystine and tyrosine being acted on only slightly during a period sufficient for nearly complete deaminization of arginine, alanine and glutamic acid. The greater proteolytic activity and the lesser deaminizing activity of Cl. histolyticum are probably the chief factors leading to the crystallization of tyrosine from protein mediums during the growth of the organism.

From the Authors' Conclusions.

Small Colony Variants or G Forms of Eberthella Dysenteriae Sonne. S. A. Koser and R. B. Dienst, J. Infect. Dis. **54**:131, 1934.

Several small colony variants, apparently similar to the G form of Hadley and to the dwarf colonies of earlier workers, were obtained from cultures of E. dysenteriae Sonne. In spite of many attempts to produce them by alterations in the environment, they were encountered in only four instances. No method was found which would promote their regular appearance. The microscopic colonies were not composed of extremely small cell elements, although a greater diversity of cell forms was to be seen than is observed in normal colonies. The fermentative capacities of the G form appeared to be qualitatively much the same as those of the original cultures when tests were made in sugar broths. However, the tendency to reversion from the G form obscured correct interpretation of the utilization of sugar in some cases. Reversion from the G form to the normal type of growth was brought about by successive transfers in broth or on agar plates and by aging in broth cultures. During the process the increase in size of the colonies was gradual, and all gradations between the two extremes were to be seen. After this process of reversion the cultures resembled the original parent strain in cultural,

morphologic and physiologic characteristics, and they were agglutinated by specific serum. Filtration tests with the small colony variants were strikingly negative, although a rather extensive series of cultural tests was applied to each filtrate. Thus, we have no evidence that these forms constitute a filtrable or virus-like stage of the organism in question. The simplest explanation, in our opinion, is that they are slow-growing variants whose cells exhibit a lower level of growth vigor than do the normal cultures.

FROM THE AUTHORS' SUMMARY.

HISTOMONIASIS ("BLACKHEAD" INFECTION) IN THE CHICKEN AND THE TURKEY. E. E. TYZZER, Proc. Am. Acad. Arts & Sci. **69**:189, 1934.

A strain of Histomonas meleagridis propagated in nutrient mediums in association with bacteria was demonstrated to be virulent after eleven months in culture but had lost its pathogenicity at the end of twenty-three months. The immunizing properties of this strain against those of a recently isolated, fully virulent strain were demonstrated in the spring and summer of 1932 by experiments on young chickens and turkeys kept under rigidly controlled experimental conditions, as well as by the practical test of rearing a vaccinated flock of turkeys for market under conditions in which nonvaccinated turkeys would not be expected to survive. This strain after another year in culture now only partially protects chickens against a virulent strain of Histomonas. The inoculation of carriers infected with an attenuated strain of Histomonas with a virulent strain commonly results in the establishment of the latter in the ceca, or "superinfection." The inoculation of the carrier with a virulent strain probably reinforces the immunity of the carrier and furnishes a basis for the continued exposure to virulent infection necessary for subsequent freedom from the disease. Rapid passages of an attenuated strain through young chickens and turkeys have failed to restore its virulence. The virulence of a culture of Histomonas is found to be dependent not on the nature of the bacteria occurring in association with the protozoon but on the biologic character of the latter, and is a quality which may be modified by long continued propagation in vitro. A second strain of Histomonas isolated on Feb. 27, 1932, and remaining fully virulent during the following summer has lost much of its pathogenicity for young turkeys after sixteen months in culture and is wholly nonpathogenic for chickens. A third strain isolated Aug. 3, 1932, was found to be fully virulent nearly ten months later. On the basis of histologic evidence it appears probable that the immunity resulting from the inoculation with an attenuated strain of Histomonas is due to slight and nonprogressive invasions of the tissues by the protozoon. Thus, while macroscopic lesions seldom appear, a study of stained sections reveals Histomonas in such minute opacities as occasionally occur and in some instances in cecal mucosa that appears quite normal to the naked eye. The suggestion is made that diminution in the immunizing properties of Histomonas under continued cultivation may be attendant on a further loss of ability to invade the tissues. In the course of long cultivation Histomonas appears not to have lost infectivity, i. e., ability to establish itself in the ceca of chickens and turkeys. No evidence has been obtained thus far that the loss of virulence is attended with greater chronicity of disease, for young turkeys recover promptly from infections with a strain formerly virulent but at present only mildly pathogenic. It is pointed out that serious obstacles interfere with the placing of the vaccination of turkeys on a practical basis.

FROM THE AUTHOR'S SUMMARY.

SENSITIVITY OF BACTERIA TO BETA AND GAMMA RADIUM RAYS. R. R. SPENCER, Pub. Health Rep. **49**:183, 1934.

The effect of radium rays (beta and gamma) on broth cultures of actively multiplying bacteria is first manifested by a retardation of growth within the first six hours after planting. When observed after twenty-four hours there may be no

perceptible difference in gross appearance between irradiated and nonirradiated cultures. After several transfers the continuously irradiated cultures may be stimulated to a more vigorous growth, and the organisms tend to display pleomorphism and to stain more deeply. Bacteria kept at sufficiently low temperatures to prevent multiplication are gradually killed by the irradiation. The lethal effect appears to be due to the beta rays. These experiments suggest rather strongly that the sensitivity or vulnerability of bacteria to radium rays is in some way associated with the activity of the cell. FROM THE AUTHOR'S SUMMARY.

SUSCEPTIBILITY OF MICE TO ROCKY MOUNTAIN SPOTTED FEVER. W. L. JELLISON, Pub. Health Rep. **49**:363, 1934.

Meadow mice have been proved highly susceptible to Rocky Mountain spotted fever. Laboratory infection in them differed from that observed in most other native rodents in that fatalities and scrotal involvement were frequent. The virus was maintained in meadow mice without apparent loss of virulence through four consecutive transfers over a period of twenty-eight days. Infected nymphal ticks transmitted the virus to meadow mice, from which noninfected larvae acquired the infection, thus demonstrating tick-to-tick transfer of the virus through this rodent as a medium. Deer mice were also found definitely susceptible, but evidently in less degree than meadow mice. No fatalities occurred among the deer mice given injections of the virus, and characteristic gross lesions were lacking in those that were put to death for passage material. House mice were distinctly resistant to the virus, and it was not possible to recover the infection from them at from seven to eleven days after injection. It appears probable that meadow mice and deer mice are natural avenues for the transfer of the virus of spotted fever from infected to noninfected ticks. In some regions, at least, it is possible that they (particularly species of Microtus) may be factors of importance in the natural maintenance and spread of the virus. This is most likely in parts of the United States in which Dermacentor variabilis is prevalent, since mice are apparently far more important hosts of the larval and nymphal stages of this tick than of those of Dermacentor Andersoni. FROM THE AUTHOR'S SUMMARY AND DISCUSSION.

THE AMERICAN DOG TICK, DERMACENTOR VARIABILIS, AS A HOST OF BACTERIUM TULARENSE. C. B. PHILIP and W. L. JELLISON, Pub. Health Rep. **49**:386, 1934.

American dog ticks, Dermacentor variabilis, in the adult stage and in the larval stage were experimentally infected with Bacterium tularense. Larvae from the ticks in the adult stage fatally infected a white-footed mouse. Resultant engorging nymphs were shown to contain the organisms in virulent form, which, in some instances, apparently cause the death of the ticks in situ; however, demonstrable infection was not produced in some of the host animals. Further evidence of generation-to-generation continuity of Bact. tularense in these ticks was secured by the injection of partial batches of eggs from two additional infected ticks. Nymphs reared from infected larvae produced fatal infections in two guinea-pigs. Infection was produced by resultant adults in separate guinea-pigs both by feeding and by injection. Tests with this and other species of ticks (to be reported) suggest that Bact. tularense is not entirely adapted to continued residence in ticks through their developmental cycle, since the ticks themselves sometimes die (apparently as a result of the presence of this organism) while still attached to the host animal and occasionally without infecting the host. Since (1) larval-to-adult and adult-to-progeny continuity of infection has been demonstrated, (2) recovery of infected ticks in nature has been reported, and (3) cases of human infection apparently associated with bites of this species have occurred, D. variabilis must be kept in mind as a possible source of human infection, especially when case histories fail to show evidence of animal contacts. FROM THE AUTHORS' SUMMARY.

Immunology

THE ACTION OF A FILTRABLE STAPHYLOCOCCAL TOXIN ON THE KIDNEYS OF RABBITS. R. H. RIGDON, A. L. JOYNER and E. T. RICKETTS, Am. J. Path. **10**:425, 1934.

A filtrable toxin from a hemolytic strain of Staphylococcus aureus produces damages to the tubular epithelium and the glomeruli when injected intravenously into normal rabbits. The most conspicuous lesion occurs in the tubules. The glomeruli are damaged, as shown by the presence of albumin, desquamated cells and red blood cells in the capsular spaces, by adhesions between the tuft and the capsule in other glomeruli and by hyaline thrombi in a few capillary loops. There is a retention of nitrogenous products in the blood of rabbits receiving staphylococcus toxin intravenously. There is no retention of nitrogenous products and the kidneys are normal in control rabbits that receive intravenous injections of sterile peptone broth.

FROM THE AUTHORS' SUMMARY.

SEROLOGICAL STUDIES ON AZOPROTEINS. K. LANDSTEINER and J. VAN DER SCHEER, J. Exper. Med. **59**:751, 1934.

A study was made of the specificity of artificial compound antigens containing aliphatic chains. Striking specificity was exhibited in the reactions of compounds with short chains containing a carboxyl group; for instance, succinic acid could be differentiated from malonic or glutaric acid which contain one fewer and one more carbon atom, respectively. With the substances containing longer chains, reactions were observed which, although specific to a certain extent, appeared to depend mainly on the general physicochemical properties of long aliphatic chains. With a limited number of substances the influence of substituents—halogen, hydroxy, amino—on the serologic specificity was investigated. By means of inhibition reactions it was possible to demonstrate the serologic specificity of cis-trans isomers such as maleic and fumaric acid.

FROM THE AUTHORS' SUMMARY.

ON THE SEROLOGICAL SPECIFICITY OF PEPTIDES. K. LANDSTEINER and J. VAN DER SCHEER, J. Exper. Med. **59**:769, 1934.

In continuation of previous studies immune serums for azoproteins made from aminobenzoyl dipeptides and tripeptides were tested with various peptide azoproteins by precipitin tests and with nitrobenzoyl derivatives of peptides by means of inhibition reactions. When examined by the latter method, the immune serums exhibited a high degree of specificity and permitted the recognition of distinctions among peptides of similar structure.

FROM THE AUTHORS' SUMMARY.

VASCULARIZATION AND SENSITIZATION OF THE CORNEA. L. A. JULIANELLE, M. C. MORRIS and R. W. HARRISON, J. Immunol. **26**:267, 281, 295 and 303, 1934.

When produced experimentally in animals trachoma does not show the pannus of the cornea which is so characteristic for the human infection. Julianelle and his associates undertook to study the factor of corneal hypersensitiveness in the pathogenesis of pannus. Of the three bacteria, Bacterium granulosis, Pneumococcus and Staphylococcus aureus, the latter exhibited the most effective sensitizing properties. Of the various methods of sensitization—(*a*) intracutaneous and (*b*) subconjunctival injections of killed or of live bacteria, (*c*) conjunctival instillations with mixtures of broth cultures and sand, (*d*) conjunctival instillations with broth filtrates, followed by instillations of bacteria, and (*e*) instillations of bacteria preceded by scarification of the cornea—the last method was the most effective. The pannus of the successfully sensitized rabbits resembled closely the pannus of trachoma. There was no relation between the corneal sensitivity of the treated

and that of the nontreated eye or between the former, the skin reactivity and the presence of agglutinins in the blood. To eliminate the factor of bacterial infection which may have played a part in the aforementioned experiments, sensitization of the cornea of the rabbit was undertaken with egg albumin and with nucleoproteins of Bact. granulosis and Staph. aureus. Sensitization was successful with all antigens, resulting in the formation of a pannus. Direct injection into the cornea proved the best route. The results were quite similar to those of the first series. Monkeys (Macacus rhesus) were successfully sensitized with live staphylococci by means of conjunctival instillations with scarifications of the cornea. A pannus developed, but it differed in details of structure and in location from the pannus of rabbits. The sensitivity was strictly localized to the inoculated eye; the other eye and the skin did not become sensitized, and the blood did not manifest agglutinins or precipitins. Bact. granulosis failed to sensitize, while crystalline egg albumin had the same effect as staphylococci.

The last paper describes experiments aiming at the transfer of the local corneal hypersensitivity from rabbits with marked corneal and skin reactivity to egg albumin and possessing a high antibody titer to the corneas of normal rabbits. Intravenous and local injections of the immune serums followed by injection of the antigen, injections of mixtures of antigen and antibody and injections of the antigen followed by antiserum produced reactions in the cornea which were interpreted as irritative and not as due to induced hypersensitiveness, although the latter conclusion was not final. Passive sensitization of skin was in certain instances successful with all three methods.

I. DAVIDSOHN.

THE ROLE OF LEUCOCYTES IN IMMUNITY TO HERPES. A. JAMUNI and M. HOLDEN, J. Immunol. **26**:395, 1934.

Both normal and immune cells aided in the inactivation of the virus in the presence of immune serum when the latter alone was present in an amount insufficient to neutralize the virus. At times results almost equally good were obtained with immune cells in the presence of normal serum, which suggests that leukocytes, or possibly tissue cells, may be even more important than the serum antibodies in active immunity to herpes. The experiments indicate at least that immune or normal phagocytic cells bring about a greater virucidal effect than can be obtained with immune serum alone.

TYPE-SPECIFIC AGGLUTININS AND ANTIBODIES IN THE SERUM OF RABBITS FOLLOWING THE INHALATION OF LIVING PNEUMOCOCCI. E. G. STILLMAN, J. Infect. Dis. **54**:339, 1934.

When rabbits are repeatedly exposed to a spray containing type I pneumococci, type-specific antibodies appear in the blood. In the experiments reported, agglutinins could be demonstrated in the serums for a short period after the course of exposures was terminated. Protective antibodies, however, persisted for long periods, even for several years. When rabbits were repeatedly exposed to a spray containing virulent type II pneumococci, protective antibodies could be demonstrated in the serums for only relatively short periods of time, while agglutinins were only occasionally found present. When rabbits are repeatedly allowed to inhale cultures of virulent type III pneumococci, type-specific immune bodies never appear in the blood. The immunity reaction exhibited by rabbits which have repeatedly inhaled a spray containing live pneumococci differs in different animals, depending to a considerable extent on the type of pneumococci employed in the experiment.

FROM THE AUTHOR'S CONCLUSIONS.

CROSS-IMMUNITY BETWEEN THE VIRUS OF BORNA DISEASE AND THAT OF EQUINE ENCEPHALOMYELITIS. B. F. HOWITT and K. F. MEYER, J. Infect. Dis. **54**:364, 1934.

Because of the difficulties involved in working with the virus of Borna disease, the prolonged incubation and the poor susceptibility of guinea-pigs to this virus

and also because of the irregular susceptibility of rabbits to the encephalomyelitis material the results given in this report are not conclusive. There is apparently no immunity to Borna disease in susceptible animals that have recovered from Californian encephalomyelitis or have shown immune reactions to the latter, while giving injections of Borna virus to guinea-pigs does not render them immune to the other strain. So far the two viruses seem to be immunologically distinct. In considering the reverse experiment, however, that is, the testing of rabbits immune to Borna disease with the virus of encephalomyelitis, immunity to the former seems to afford protection to the other type of virus. This, however, may be more apparent than real, because by the time the rabbits had been immunized to the Borna disease and tested for immunity several months had elapsed. The animals had grown in the interval and were undoubtedly still less susceptible to a virus that does not regularly produce the disease. It may be stated in conclusion that from certain clinical, histologic and immunologic observations, it seems tentatively logical to assume that the equine encephalomyelitis described in California is distinct from that known by European writers as Borna disease.

FROM THE AUTHORS' CONCLUSIONS.

IMMUNIZATION OF GUINEA-PIGS TO THE VIRUS OF EQUINE ENCEPHALOMYELITIS. B. F. HOWITT, J. Infect. Dis. **54**:368, 1934.

Different methods of active immunization to the virus of equine encephalomyelitis were tried in guinea-pigs, using suspensions of virus attenuated by chloroform, phenol, glycerite of phenol or solution of formaldehyde, respectively. The results were largely unsatisfactory, although immunity was always present in animals that survived intracerebral injections of live virus. On the other hand, successful immunization without fatalities due to vaccination was obtained in several groups of guinea-pigs by simultaneous administration of serum and virus followed by one or two doses of a suspension of active virus alone. Injections should be made at weekly intervals, and the correct proportions of immune serum and virus should be determined before use by intracerebral inoculation of guinea-pigs. Immunization may be obtained with small doses of live virus alone when given intramuscularly, subcutaneously or intradermally, although fatalities due to vaccination may occur. The virus was recovered from the salivary glands of two of thirty-three immunized guinea-pigs, two weeks and one month after vaccination, respectively, but was not present in the brain. Immunity may be retained in guinea-pigs for at least six or seven months after the animals receive the last injection of virus, even though only one dose is given. The duration of immunity is not coincident with the development of antiviral substances in the blood of immunized or of recovered guinea-pigs, as demonstrated by the in vitro neutralization test. The presence of such antibodies is variable; usually they are lacking, except after hyperimmunization with active virus. They may then be demonstrated within twenty-four hours after the stimulating dose is given. Immunity may be conferred on young guinea-pigs born either of two immune parents or of an immune mother, but not on those born of nonimmune parents or of a nonimmune female and an immune male. This immunity was demonstrated two and three days, two weeks and one month, respectively, after birth, while the animals were still with the mothers.

FROM THE AUTHOR'S SUMMARY.

OPTIMAL AGGLUTINATION: THE SIGNIFICANCE OF THE DIFFERENT RATIOS OF SERUM TO BACTERIA. J. T. DUNCAN, Brit. J. Exper. Path. **15**:23, 1934.

Duncan carried out a series of agglutination tests with a single strain of Bacterium dysenteriae Flexner. Complete agglutination at the highest serum dilution occurs with an optimal concentration of salt which may vary with different species of bacteria.

JACOB KLEIN.

THE DURATION OF PASSIVE IMMUNITY TO DIPHTHERIA. E. G. M. JONES and J. D. KERSHAW, Brit. M. J. **2**:969, 1933.

Passive immunity to diphtheria was obtained in a highly satisfactory proportion (97.9 per cent of all children tested and 100 per cent of those under ten years) of children with positive Schick tests by the injection of 500 units of diphtheria antitoxin. In adults and adolescents over 15 a larger dose is probably necessary. The duration of this immunity is at least fourteen days and in the majority of cases (94.4 per cent) extends to twenty-one days. The incidence of diphtheritic infection in passively immunized patients at the times stated suggests that it is unwise to regard this form of immunity as lasting longer than three weeks.

FROM THE AUTHORS' CONCLUSIONS.

THE INFLUENCE OF TESTICULAR EXTRACT ON THE ABSORPTION OF DIPHTHERIA ANTITOXIN. D. MCCLEAN, W. T. J. MORGAN and G. FAVILL, J. Path. & Bact. **38**:253, 1934.

Testicular extract is unlikely to be of use in accelerating the rate of absorption of diphtheria antitoxin, since absorption by the intramuscular route, which is normally more rapid than by the subcutaneous route, is not hastened by the addition of the extract.

FROM THE AUTHORS' SUMMARY.

IMMUNE SERUM AGAINST BODO CAUDATUS. M. ROBERTSON, J. Path. & Bact. **38**:363, 1934.

The serum of rabbits given injections of Bodo caudatus, a flagellate protozoon, caused some degree of immobilization of the bodos, also agglutination and gradual death. The addition of guinea-pig serum to the heated immune serum resulted in lysis of the bodos.

VIRULENCE OF TYPHOID BACILLUS AND RESISTANCE TO O ANTIBODY. A. FELIX and R. M. PITT, J. Path. & Bact. **38**:409, 1934.

The virulence of the typhoid bacillus is intimately associated with its resistance to the action of the O antibody. Inagglutinable strains are highly virulent while agglutinable strains are of low virulence. The inagglutinability is a property of the living bacterium and is annulled as soon as it is killed. The resistance to O agglutinins is also suppressed by growth on phenol agar; simultaneously the virulence is reduced. While roughness denotes low virulence, the mere presence of smooth O antigen does not define high virulence. The nature of the factor present in virulent strains that renders the smooth O antigen resistant to O antibody is as yet unknown.

FROM THE AUTHORS' SUMMARY.

EVOLUTION OF TUBERCULIN SENSITIVITY. A. BOQUET and J. BRETEY, Ann. Inst. Pasteur **52**:252, 1934.

The length of the preallergic period in a guinea-pig infected with virulent organisms varies in inverse relation to the dosage. Hypersensitivity is established and increases in intensity without fever or other symptoms indicating advancing infection. Although the preallergic period is lengthened with organisms of diminished virulence, the change is not great. The state appears to depend less on the intensity of the cellular reactions and the extent of the lesions than on the antigenic qualities of the organisms, and this in turn is not related to the virulence. Dead organisms induce a slower reaction than do living cells. Sensitivity reaches a high level during the first stages of infection and progresses relatively slowly thereafter. Animals inoculated with attenuated organisms develop allergy slowly and retain the state more in proportion to the duration of chronic infection than in proportion to the activity of lesions. Thus dead organisms induce a state which disappears after some months. It seems likely that the allergic state rests on the

retention of antigenic complexes in the protoplasm of cells of the reticulo-endothelial system and elsewhere rather than on continuous diffusion of such material. Such a hypothesis seems especially to be indicated in allergy arising from the injection of dead bacilli.

FROM THE AUTHORS' CONCLUSIONS.

BLOOD GROUPS AND IMMUNITY. HORST BINHOLD, Deutsche med. Wchnschr. **60**:468, 1934.

There is no evidence of any connection between the blood groups and immunity. The blood grouping appears to be independent of the activities of the reticulo-endothelial system on which largely depends the defense against microbes.

THE SCHICK AND DICK REACTIONS AND THE NASOPHARYNGEAL BACTERIAL FLORA OF NJENZEN ON THE KOLGUJEW ISLAND. W. N. ASBELEW and A. A. MARGO, Zentralbl. f. Bakt. (Abt. 1) **126**:212, 1932.

The authors tested 103 persons of different ages on the Kolgujew Island (69 degrees north latitude) for Schick and Dick reactions. Diphtheria and scarlet fever are not known to occur among these people. The Schick test was negative in all but one, an 8 year old girl. Similarly the Dick test was negative in all but one instance and there it was doubtful. Skin anergy was excluded, as a group of Njenzen living on the mainland (33 persons tested) showed positive Schick tests in 12 per cent of cases and positive Dick reactions in 30 per cent. Tests for the presence of diphtheria antitoxin by Römer's method were not made.

No diphtheria carriers were found among 168 residents of the island who were examined. Streptococci were found in 84 per cent of the instances, hemolytic types in 3 cases.

PAUL R. CANNON.

THE ANTISPIROCHETAL IMMUNE SERUMS. HANS GOTTLIEB, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:222, 1933.

The immune serums produced in rabbits by inoculation with Spirochaeta pallida reacted also with alcoholic extracts of brain tissue and with brain lecithin. The antibodies which reacted with the brain extract could be separated by means of their lesser thermostability from the antibodies which reacted with the homologous antigens. Immune serums which were produced in guinea-pigs by inoculation with S. pallida did not react with brain tissue. Spirochetes contain antigenic substances of protein and of lipoid character. The lipoid fraction is the one which is shared with the brain tissue.

I. DAVIDSOHN.

THE SPECIFICITY OF FIBRINS. HANS J. FUCHS, M. VON FALKENHAUSEN and H. KOWARZYK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:233, 1933.

Fuchs and associates applied the microchemical determination of nonprotein nitrogen for the diagnosis of infectious diseases much as they had used it for the diagnosis of malignant conditions. The specific antigenic substance of the syphilitic infection is present in the fibrin and in the serum of patients. Precipitates prepared from extracts of cultures of Spirochaeta pallida with trichloracetic acid could be used interchangingly with the fibrin of serum of syphilitic patients for the diagnosis of the disease. Any one of the three substances produced an increase in the nonprotein nitrogen when mixed with the serum of syphilitic patients. The tuberculous antigenic substance was similarly found in the fibrin or serum of tuberculous patients or in preparations of old tuberculin Koch. The syphilis-specific substances in the serum of infected persons come therefore, in the light of these results, not from the tissues of the host but from the spirochetes, as the specific substance in the serum of persons with tuberculosis comes from the tubercle bacilli.

I. DAVIDSOHN.

STAPHYLOLYSIN STUDIES: II. J. FORSSMAN, Acta path. et microbiol. Scandinav. **11**:214, 1934.

From this and earlier work on staphylolysins it appears that as a rule no absorption of staphylolysin can be observed on the part of red blood cells susceptible to the lysin, but that the lysis occurs immediately after the union of the lysin with the red blood cells, hence only the end-results of the reaction are seen.

Tumors

EXTRAGENITAL CHORIONEPITHELIOMA IN A MALE. A. R. KANTROWITZ, Am. J. Path. **10**:531, 1934.

A report of a primary teratoma of the anterior mediastinum containing chorionepitheliomatous elements in a man aged 22 years is presented. The tumor invaded the superior vena cava, studding both lungs with chorionepitheliomatous nodules. There were no metastases in the other organs or lymph nodes. The genital tract showed no tumor nodules. The testicles revealed no tumor nodules. The tumor contained teratomatous and chorionepitheliomatous elements. Only chorionepithelioma was found in the pulmonary metastases. Marked interstitial cell hyperplasia of the testes was present. The Aschheim-Zondek test was positive in both the urine and tumor tissue extracts.

FROM THE AUTHOR'S SUMMARY AND CONCLUSIONS.

MULTIPLE HEMANGIOBLASTOMAS OF THE SPINAL CORD WITH SYRINGOMYELIA (LINDAU'S DISEASE). A. WOLF and S. L. WILENS, Am. J. Path. **10**:545, 1934.

A case of multiple hemangioblastomas of the spinal cord forming part of Lindau's syndrome is presented. These intramedullary tumors were associated with a syringomyelia and syringobulbia. The other lesions were a cystic cerebellar hemangioblastoma, congenital cysts of the pancreas and kidneys, a benign hypernephroma of the left kidney, a suprarenal rest in a retroperitoneal lymph node and three paragangliomas of the left suprarenal gland.

FROM THE AUTHORS' SUMMARY.

THE GRADING OF EPIDERMOID CARCINOMA. OLIVE GATES and SHIELDS WARREN, Surg., Gynec. & Obst. **58**:962, 1934.

One arbitrary pattern for grading tumors is not sufficient. Locality, with due regard for the character of the normal epithelium of the part, must be considered. Of the various factors concerned with grading, cellular differentiation is the most important, and in epidermoid carcinoma it parallels the degree of keratinization, but increase of mitotic activity, especially abnormal mitosis, increased variation of cell size and shape, and accentuation of the tendency to infiltrate tissue are indicative of the higher degrees of malignancy. Stromal changes are of no importance in grading. The more complicated methods of grading, such as that of Hueper, have proved of no greater value than the simpler ones. The authors distinguish only three grades of malignancy and arbitrarily choose the least differentiated portion for grading purposes, at the same time making allowances for the presence of a higher degree of maturity elsewhere in the tumor. Any practical value of grading rests on the clue it gives to the subsequent behavior of the tumor, and this, in epidermoid carcinoma, tends to be determined by the most active portion. The frequency of various degrees of malignancy was studied in 5,052 epidermoid carcinomas removed from 4,987 persons. The conclusion reached was that grading should not be used as a guide in individual prognosis, although it is an aid in determining group prognosis and in estimating the probable radio-

sensitivity of a given cancer. Epidermoid cancers developing in sites such as the skin and lip where the clinical malignancy is low tend to be of low histologic malignancy, while those springing from the buccal cavity, uterine cervix and respiratory tract are of high malignancy. Sex and age have no influence on histologic malignancy. Metastases tend to have the same grade as the primary tumor. Histologic malignancy is not greater in cancers of multiple malignancy than in single carcinoma.

W. C. HUNTER.

NEUROGENIC TUMORS OF THE SYMPATHETIC SYSTEM IN CHILDREN. J. W. S. BLACKLOCK, J. Path. & Bact. **39**:27, 1934.

Of a series of malignant tumors in children those arising from the sympathetic system were fourth in order of frequency. In the eighteen tumors with this origin different stages in the development of the cells were observed, from one composed of the most primitive type of sympathetic cells (sympathogonia) through an intermediate group in which many of the sympathogonia had differentiated into sympathoblasts and small ganglion cells to one composed only of mature ganglion cells. Indeed, in certain tumors transitional stages could be traced from small embryonic cells to small and mature ganglion cells. In the remarkable (and indisputable) case described by Cushing and Wolbach (1927) this was actually observed to occur during the life of a child in whom a tumor of the dorsal region was diagnosed histologically as a sympathicoblastoma in the early years of life while ten years later when the tumor was removed surgically it had become an adult ganglioneuroma. The intermediate group was the commonest type in the series, which is in agreement with most of the reported cases. I have suggested a simple scheme for the classification of these growths according to the degree of differentiation of their cells.

FROM THE AUTHOR'S SUMMARY AND DISCUSSION.

ON LYMPHO-EPITHELIOMA OF THE NASOPHARYNX AND TONSILS. D. F. CAPPELL, J. Path. & Bact. **39**:49, 1934.

Twelve cases of malignant disease of the nasopharynx, tonsils and pharynx have been studied and are believed to be of epithelial origin, arising from the specialized epithelium of the pharyngeal lymphoid tissues. The value of silver impregnation of the reticulum as a means of demonstrating the structure of such growths is emphasized. These tumors show distinctive clinical and pathologic features and may justifiably be separated from other neoplasms under the name of "lympho-epithelioma." Two main types of histologic structures have been recognized, the one corresponding to the classic lympho-epithelioma of Regaud and the other to the lympho-epithelioma of Schmincke. It is shown that these are not different types of neoplasm but represent merely quantitative differences in the mode of growth and spread of the tumor cells. Evidence for regarding transitional cell carcinoma of the nasopharynx and tonsil as a different form of neoplasm from lympho-epithelioma is not definitely established in the present observations, and it is believed that the two are at least closely related. Lympho-epitheliomas are highly radiosensitive, and the value of radiation therapy in contrast to surgical excision is clearly demonstrated in the present series of cases.

FROM THE AUTHOR'S SUMMARY AND CONCLUSION.

SARCOMA OF THE SPLEEN. J. W. MCKEE, J. Path. & Bact. **39**:83, 1934.

Two examples of primary new growth of the spleen are recorded and are classed as lymphosarcoma. The clinical picture in some of these cases may closely resemble untreated pernicious (addisonian) anemia.

FROM THE AUTHOR'S SUMMARY.

THE SPECIFICITY OF THE CHEMICAL AND SEROLOGIC FRACTIONS OF EXTRACTS OF CANCER TISSUE. HERMANN LEHMANN-FACIUS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:99, 1934.

The so-called phosphatide fraction (benzene-soluble and acetone-insoluble fraction) and the so-called fatty acid fraction (benzene-soluble and acetone-soluble fraction) of the alcoholic extract of cancerous tissue differed in their antigenic properties in vivo and in vitro. Many immune serums produced in rabbits inoculated with mixtures of the phosphatide fraction and hog serum reacted specifically with phosphatide fractions of cancerous tissues in the complement-fixation and still better in the precipitation test. Some of the phosphatide fractions and the immune serums produced by them lacked such specificity, but they, too, possessed the ability to react specifically with carcinomatous antiserums or carcinomatous tissue extracts after the general nonspecific lipoids were removed by means of absorption with lecithin. Such phosphatide fractions reacted strongly in precipitation tests with immune serums produced by immunizing rabbits with fatty acid fractions of carcinomatous tissues but did not precipitate antiserums produced with the phosphatide fractions. The antiserums produced with specific phosphatide fractions lost none of their reactivity when absorbed with lecithin and precipitated exclusively with phosphatide fractions of the extracts of cancerous tissues.

I. DAVIDSOHN.

Medicolegal Pathology

SUDDEN DEATH. L. HAMMAN, Bull. Johns Hopkins Hosp. **55**:387, 1934.

Statistics are cited which indicate that about 91 per cent of sudden deaths from natural causes are due to disease of the cardiovascular system, such as heart failure, hemorrhage, thrombosis and embolism. Sixty-five per cent of all cases are due to sudden heart failure; 21 per cent to hemorrhage; 5 per cent to thrombosis and embolism. Of the deaths from sudden heart failure, 65 per cent occur with disease of the coronary arteries, 21 per cent with valvular heart disease, 10 per cent with myocardial disease and 3 per cent with cardiac hyperthrophy. Syphilis of the aorta is a frequent cause of sudden death, occurring in about 20 per cent of all cases due to natural causes. The most important natural causes of sudden death and their relative incidence are listed as follows:

	Per Cent
Disease of the coronary arteries (including coronary occlusion due to syphilitic aortitis)	40
Aneurysm of the aorta	12
Valvular heart disease	12
Myocardial disease	8
Cerebral hemorrhage	8
Pulmonary embolism	5
Pulmonary hemorrhage	5
All other causes	10

APPLICATION OF THE METHOD OF PRESERVING UNFIXED TISSUE BY FREEZING TO FORENSIC MEDICINE. G. SCHRADER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:172, 1934.

The method rests on the discovery that the albuminous materials of the cells and tissue fluids maintain their adhesive properties in unfixed preparations, and that these properties are preserved in the frozen state so that they manifest themselves when the section thaws. Sections thus attached by their own albumin can be stained and treated in various ways so that they combine the virtues of paraffin and frozen sections. The method was applied to fresh postmortem material and was found helpful in establishing a diagnosis and in determining the tissues to be preserved for further study. Partly decomposed bodies offered no difficulties with this method, as was proved in a corpse exhumed three weeks after death. The lung of this body had better adhesive powers than a normal lung. A large amount

of precipitate from solution of formaldehyde may interfere with the adhesive qualities of the tissues from some bodies, however. Foreign bodies were studied satisfactorily by this method. Powder granules were readily seen along bullet wounds, threads driven in by wounds from blunt force were visualized, and amniotic fluid and meconium were demonstrable in the lungs of new-born children. The method proved especially valuable in these instances because fat and other stains could be made on tissues from the same block. With a little practice, serial sections could be made. The histologic changes of the skin in deaths from electricity, burns and scalds could be distinguished. Even in severe burns the sticking qualities of the deeper layers of the skin were preserved, and they were absent only where extensive charring was present. The contents of blebs, the result of scalds, were well preserved, so that leukocytes could be seen in them. Dry skin was found to adhere well if, before cutting, it was soaked in a mixture of blood serum and sodium chloride (physiologic solution of sodium chloride) in the ratio of 2:1. Skin which had been in water as long as nine weeks still was suitable for study.

GEORGE RUKSTINAT.

DEMONSTRATION OF GROUP-SPECIFIC SUBSTANCES IN ORGANS FIXED WITH SOLUTION OF FORMALDEHYDE. I. MOHARREN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:197, 1934.

Preliminary tests revealed that undiluted solution of formaldehyde takes red blood cells, whereas moderately diluted solution of formaldehyde inhibits both iso-agglutination and isohemolysis. Only with dilutions higher than 1:2,000 can one be certain that solution of formaldehyde will not affect the isoreactions. For the demonstration of group-specific substances in organs fixed in solution of formaldehyde, Moharren recommends the use of aqueous extracts prepared by boiling the finely divided tissues in distilled water. The extract is evaporated to dryness, and if there is no longer any odor of formaldehyde, the extract is redissolved in physiologic solution of sodium chloride. Otherwise, the process of extraction and evaporation is repeated as many times as necessary, the insoluble residue being separated each time by centrifugation and discarded. The presence of group-specific substances in the aqueous extract is detected by the ability of the extract to inhibit iso-agglutinins, and, in the case of property A, also by its ability to inhibit sheep lysin. Most of the tests were made on material from eight to fourteen days old. On much older material, the possibility of deterioration of the group-specific substances must be borne in mind.

A. S. WIENER.

BLOOD GROUPING ON SMALL QUANTITIES OF BLOOD STAIN. C. HALLAUER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:206, 1934.

If possible, blood stains should always be examined for both agglutinogens and agglutinins. If only a small quantity of blood is available, it may be possible to do only one of the tests, in which case that for agglutinins is to be preferred on account of the greater stability of these substances. Hallauer recommends preparation of aqueous extracts of the blood stains in such cases, then testing for the properties A and B by the ability of the extract to inhibit the iso-agglutinins. Whereas this method was successful with the properties A and B, it failed when applied in tests for the properties M and N.

A. S. WIENER.

HEMORRHAGIC EXTRAVASATION INTO CERVICAL LYMPH NODES IN DEATHS FROM VARIOUS CAUSES. L. JANKOVICH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **23**:314, 1934.

Hemorrhage into the lymph nodes of the neck may occur not only in death from hanging but in deaths from various other causes. Such hemorrhages have no common cause or explanation. As in hanging, they occur during the last struggles of life. Great care must be used in their interpretation as vital phenomena.

FROM AUTHOR'S SUMMARY.

Society Transactions

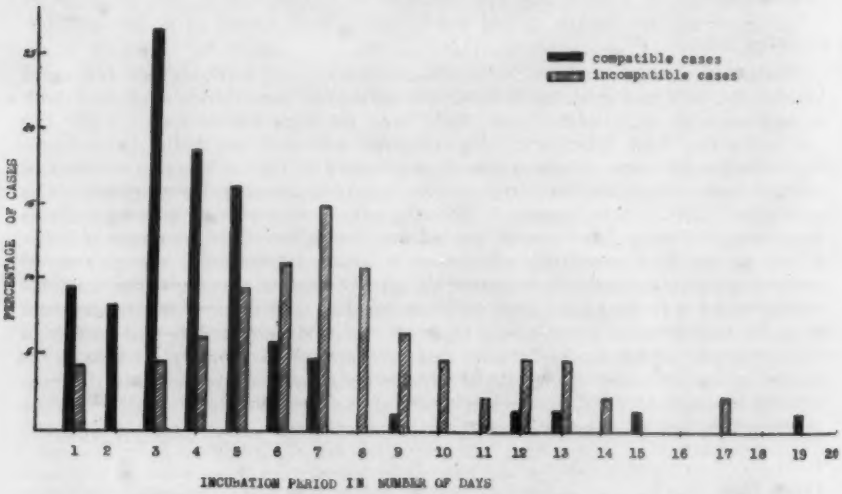
NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 28, 1933

PAUL KLEMPERER, *President, in the Chair*

BLOOD GROUPS AND THERAPEUTIC MALARIA. SILIK H. POLAYES and IRVING M. DERBY (by invitation).

A series of 127 patients with dementia paralytica treated by injection of malarial blood were studied in order to determine (*a*) the effect of the injection of compatible or incompatible blood on the period of incubation; (*b*) the occurrence of immediate or delayed reactions to incompatible malarial blood, and (*c*) the frequency of occurrence of so-called primary fever. The following conclusions may be drawn:



The effect of blood groups on the incubation period of therapeutic malaria (intravenous) in dementia paralytica.

Period of Incubation.—(The data can be studied best from the accompanying graph.) The average period of incubation is 4.3 days when the malarial blood injected is compatible and 8.18 days when it is incompatible with the recipient's serum. That this difference is significant was proved by statistical analysis.

Wide variation of the period of incubation was noted in the group receiving compatible as well as in that receiving incompatible blood. The differences may be ascribed to factors other than compatibility or incompatibility of blood.

Incompatibility Reactions.—With regard to untoward postinoculation reactions, it was not possible to determine with certainty that they were due to incompatibility between the donor's and the recipient's blood. Other possible factors are mentioned which may be responsible for these reactions.

Primary Fever.—Primary fever occurred in only 15 per cent of the patients receiving compatible malarial blood. This figure is much smaller than those found

by previous investigators. The difference is perhaps due to the fact that it is difficult to recognize this phenomenon because the postinoculation temperature curve is frequently too regular to conform rigidly to the definition of primary fever.

A Case of Nonlipoid Histiocytosis, with Necropsy. Nathan Chandler Foot and Charles T. Olcott.

During the past decade a condition known variously as "aleukemic reticulosis," "reticulo-endotheliosis" and so forth has gradually been defined in the German literature, the reports coming from German and Russian sources; it has been described only once in the American journals during that time. This is due either to oversight or to the rarity of the incidence of the disease in this country; it seems more likely that it is the result of unfamiliarity with the condition on the part of American pathologists.

Clinically it is characterized by a purpuric eruption all over the body and a paucity of typical symptoms. Physical signs include an invariably enlarged spleen and an enlarged liver in a child, while in an adult this may or may not be a concomitant sign. Osteoporosis is frequently found on roentgenologic examination, but is as frequently missed. Bone cysts or areas of rarefaction have been reported in a number of cases.

At necropsy the thymus is the site of small abscess-like areas of softening, identifiable with degeneration of Hassall's bodies. Besides the petechiae in the skin, there are usually petechial hemorrhages in the epicardium and sometimes the pleurae. There is usually a generalized lymphadenopathy; the liver is usually enlarged, always fatty in children, and shows early cirrhosis in any case. The spleen is also enlarged and firm. The bone marrow shows overgrowth with invasions of the substantia spongiosa of the cancellous bone. Microscopically these changes are all referable to an overgrowth of the mononuclear cells of the reticulo-endothelial system, most marked in the spleen, lymph nodes and bone marrow. The cells are actively phagocytic for erythrocytes and do not show lipoid droplets. There are occasional giant cells in the sections, resembling sometimes the Reed-Sternberg type, sometimes the Langhans type and sometimes megakaryocytes. Their origin is uncertain, but they seem to be produced from the reticulo-endothelium. The blood picture is sometimes that of a monocytic leukemia; sometimes other leukemias have been reported in conjunction with the disease. It differs from "retothelial sarcomatosis" in that its cells are well differentiated and not neoplastic and no true tumor foci are found.

A case occurring in a girl 2¼ years of age is reported. It fulfils all the criteria for a diagnosis of the condition under discussion. No leukemia is noted; there is a history of frequent mild infections of the upper respiratory tract as well as a family history of asthma and nosebleed that is striking. After a splenectomy which brought the case to our attention, the condition of the spleen being typical of this disease, the patient improved temporarily, only to die a few months later with a recurrence of the purpuric symptoms, the development of osteoporotic changes and a cystic degeneration of several intervertebral disks.

The spleen weighed 310 Gm. and was typical; the liver showed marked fatty infiltration and early cirrhosis; the lymph nodes about the pancreas and portal area of the liver were enlarged and their condition typical under microscopic examination; the bone marrow showed foci of reticulo-endothelial proliferation and some phagocytosis. Petechiae were found in the epicardium, and areas of softening in the thymus were also present. The brain presented a marked increase in microglial elements and numerous rod cells in the frontal lobes, a feature hitherto not reported.

We are inclined to side with those who believe the condition to be a response to an infective agent, rather than with those who believe it to be an aleukemic phase of monocytic leukemia.

DISCUSSION

Charles T. Olcott: It might be of interest that there was a history of hay fever or asthma in the paternal grandmother, the father and the patient, and a history of frequent epistaxis in two paternal granduncles and the father.

SHELDON A. JACOBSON: I am interested in an incidental point: The condition of these intervertebral disks presents an interesting problem in statics. According to the more recent conception of the intervertebral disk the entire pressure of the body weight is borne by the nucleus pulposus, whereas the remainder of the disk is there for the purpose of resistance to stretching. Some of these nuclei are gone. I should like to know something about the edges of those disks (if they were noticed particularly), because a priori they do not seem able to support the weight of the upper part of the trunk and head.

PAUL KLEMPERER: This is the first time reticulo-endotheliosis has been discussed before the society. I agree with Dr. Foot and Dr. Olcott that their case belongs to a certain type in this very indefinite group, described chiefly in the German literature. The term "nonlipoid histiocytosis," though a little long, definitely denotes the evolution which the immature reticulum may take in some cases, and probably this case is of a much more clearcut type than are most of the cases which have been described in the literature as reticulosis. Dr. Foot has correctly emphasized that reticulosis embraces most probably a considerable number of cases which could be pigeonholed much better under leukemia or reticulosarcomatosis in one group in which the immature reticulum cell is developing into a hematic cell, while the case of nonlipoid histiocytosis is an instance in which this immature mesenchymal cell has matured into a cell which has to be regarded as inflammatory or, let me say, using a more general term, into a digestive form. To the group of reticulosis belong only those instances in which the reticulum cell in its most immature form proliferates diffusely throughout the body. I think that there are only very few such cases. Certainly one case in the Russian literature (Tschistowitsch and Bykowa) corresponds to this type. I think Dr. Richter's case belongs to the hematic type of cell proliferations in which the type cell can be recognized as a hematic cell, though I do not know whether Dr. Richter will agree to that.

Of course there still exists the problem of the relation in which the type of case described by Dr. Foot and Dr. Olcott stands to Hodgkin's disease, that is, the more immature hyperplastic forms of Hodgkin's disease. I do not think that the condition in this case should be diagnosed as Hodgkin's disease, but there might be similar conditions which could be looked on as belonging to the indefinite group called atypical Hodgkin's disease.

In my recollection of cases which had some relation to this type of reticulosis, I do remember two instances which closely resembled that described tonight. It is interesting that both cases distinctly presented features of an infectious disease; clinically they were regarded as chronic septicemia. In that respect I should like to ask Dr. Foot whether he has not observed instances of chronic infections—let me use the term "chronic septicemia"—in which similar proliferations, though not so widespread, were to be observed. I have a distinct recollection of at least one case, that of a woman in the early forties, in whom the spleen presented a picture similar to the one which Dr. Foot showed here. I was also reminded of one of the cases reported in the European literature, the case of Akiba, in which the histologic picture closely resembled that presented here.

I think it is a most interesting form of, I should not say a new disease, but a peculiar reaction of the immature mesenchyma with maturation in this case, and the question as to the etiology still remains. I understand that except for the observations in the wound the results of the bacteriologic examination were negative. In the case of Akiba microbes were found. In both of my cases, which I think belong to this group, no bacteria were found.

NATHAN CHANDLER FOOT: As far as the state of the intervertebral disks is concerned, I think I had better refer Dr. Jacobson to Dr. Olcott, as he made the postmortem examination of the body.

Dr. Klemperer's discussion has been most interesting, as he has brought up a number of points which I should have liked to mention in the paper had I had a little more time, and this gives me the opportunity to do so. We used the term

"nonlipoid histiocytosis" because this is not a reticulosis; that would imply an increase in the reticular fibers, rather than in the cells, so that I think the term "reticulosis" should be rejected; reticulo-endotheliosis would be a different thing; that, of course, would be quite proper.

The fact that the cells remain true to type, as Dr. Klemperer brought out, seems a very important feature in connection with the theory that the disease is due to an infectious agent; in other words, all the cells that we found were acting like mature macrophages or phagocytes and were not behaving like tumor cells. The immature cells, when one sees them, constitute generalized lymphosarcoma; that occasionally comes up. There was such a case at the New York Hospital last year, in which there were numerous reticulosarcomas distributed all over the body. In some cases they were subcutaneous; they were in many of the internal organs and even in the meninges. In every case the cells were very immature, and mitotic figures were frequent. There were present all the criteria of a malignant neoplasia. The whole problem is difficult because the cells are difficult to interpret. Observers are not entirely in accord as to the origin of the macrophages as yet. They are getting a little further along the road, but there is still much discussion as to where the macrophage comes from, and whether all the aliases of the macrophage refer to the same cell or several cells which are similar, and as long as there is that doubt there is going to be doubt in tackling a disease in which the macrophage plays a stellar rôle.

As far as Hodgkin's disease was concerned, at the time the spleen was removed in this case we found large numbers of eosinophils, a good deal of fibrosis in some parts of the spleen, and these giant cells which are not entirely unlike the Reed-Sternberg cells, so that in my description I made a notation of this, and said that on account of the other features I did not consider the condition to be Hodgkin's disease, but we did consider the possibility of Hodgkin's disease carefully. There was a definite resemblance to an atypical Hodgkin's disease in some respects, particularly the large numbers of eosinophils, the giant cells and the slight increase in connective tissue. I have seen a good many cases of chronic infection, particularly in children, in which pseudoleukemic foci were found. One would be almost sure one was dealing with a chloroma, and yet with the history of the case, the fact that the child had had definite diphtheria or scarlet fever ante mortem and no history of leukemia one could rule it out.

In the bacteriologic examination of this case, the hemolytic Staphylococcus aureus, which is a very common organism, was recovered from the cardiac blood as well as from the wound and from the fauces when the child had pharyngitis, and also a hemolytic streptococcus, so that there was some agreement in the cultures taken from various parts of the body.

CHARLES T. OLCOTT: In reply to Dr. Jacobson's question with relation to the vertebral column, this child clinically had kyphosis six weeks before death, and the question arose as to whether it might not be Pott's disease. At autopsy there was no rigid deformity, and the intervertebral disks were as Dr. Foot has described, usually liquefied, except for their capsules.

HISTOLOGY OF PAGET'S DISEASE OF THE BONE. VERA B. DOLGOPOL.

The histologic observations in three patients with Paget's disease of the bone (a man, 58 years old, and two women, 60 and 74 years old) included almost all the characteristic features of this disease.

In the early stage of the disease the process consists in osteoclasis of the wall of the haversian canals.

In the advanced stage the affected bones show mosaic-like trabeculae composed of irregular pieces of lamellar bone outlined by thick, short, scalloped cementing lines. Osteoid borders with a row of osteoblasts are seen on some trabeculae. Osteoclasis is active. The bone marrow between the trabeculae is fibrofatty. In long bones the marrow of the central canal may undergo a myeloid transformation as

the result of fibrosis of blood-forming marrow in other bones. Fibrous changes in the bone marrow seem to begin from the endosteum of trabeculae already showing changes characteristic of Paget's disease. Endarteritis was observed in two cases in arteries of the periosteum of long bones and in those of the fibrous bone marrow of the skull. Formation of primary fibrous bone by precipitation of calcium in the ground substance of the skull was observed in one skull. Besides wandering phagocytic cells, clusters of round fixed phagocytes, with a small nucleus and with refractile granules in the cytoplasm, were observed in the bone marrow in two cases (in the femur and in the skull).

Parathyroid glands were examined in two cases. They showed microscopic pictures normal for the age of the patients.

DISCUSSION

HENRY L. JAFFE: Dr. Dolgopol's paper is thoroughly instructive. I should like to say a few words about the mosaic which she so clearly emphasized. Of course to Schmorl goes the credit for having brought into relief the diagnostic value of the histologic examination for, and the significance of, the mosaic picture. I think that until he emphasized it the general impression was that, given a histologic slide, one could not differentiate very easily or with any great degree of reliability between Paget's disease and any other of the diseases of bone, except rickets and osteomalacia. Of course that is not true now, in view of the great importance that histologic examination plays in diagnosis. It is interesting, however, that if one reads Paget's original article the histologic description of the mosaic is there, and the histologic description was given by Goodale. In fact, all through the literature of Paget's disease one finds the mosaic clearly described, but its significance was not grasped until recently. In a paper by Knaggs, the English surgeon, there is pictured and also described histologically what he calls the internal curvilinear markings in the bones in Paget's disease. The meaning of the mosaic is probably of great importance histologically, and if one clearly understood why the mosaic is produced in Paget's disease, one would know a little more as to why Paget's disease is produced in the human being, or how it comes to originate. On that point my colleagues and I have tried to carry out some experiments in the rat. We started with the idea that the mosaic naturally is the result of intermittent rapid resorption and deposition of bone. That must be the impression one gets from the mosaic picture. We thought that if we could produce in an animal rapid resorption and rapid deposition of bone at the same time, or intermittently, we might be able to build up a mosaic picture. We gave rats large quantities of parathyroid extract, and at the same time, because the rat can stand parathormone in large doses without succumbing to hypercalcemia, we gave the rats rather large amounts of supplementary calcium in their diet. We could produce pictures which, while not exactly simulating the Paget mosaic, looked like that architecture. There were furthermore induced a marked thickening of the cortex of the bone and a marked metaphyseal osteosclerosis. Certainly if we are to go any further in understanding Paget's disease from the point of view of pathogenesis we shall have to accept that there is nothing like a deficiency of calcium associated with it.

DAVID SEECOF: In the last slide in the column by Schmorl, in the table presented by Dr. Dolgopol, there was a marked discrepancy between the right and left femur involvement. I wonder how that can be explained.

VERA B. DOLGOPOL: I don't know how to explain it. There is no reason to believe that the right side carries the weight more than the left.

DAVID SEECOF: I wonder whether it was not due to the fact that one side was examined more often than the other.

VERA B. DOLGOPOL: I do not think so. Schmorl undertook the work systematically. In cases in which he did not examine certain bones, for example, those of the forearm, he stated that fact. If he had examined the right femur more often than the left, he would have mentioned it.

THE PIGMENTED MOLE AS A TACTILE ORGAN. ITS PLACE IN THE EVOLUTION OF HAIR FOLLICLES. GEORGE F. LAIDLAW and MARGARET R. MURRY (by invitation).

Our point of departure is Masson's demonstration of nerve fibers and meissnerian tactile corpuscles in pigmented moles, confirmed by Stout, Foot, Ewing and Miescher. Photomicrographs of silver-stained sections were presented showing the nerve fibers in pigmented moles terminating as tiny end-bulbs on the nevus cells just as they terminate on the tactile cells of the epidermis and the hair follicles. Nerve trunks were shown dividing, some fibers ending on the tactile cells of a hair follicle and others ending in contact with nevus cells. Other sections showed pigmented moles filled with meissnerian tactile corpuscles. The pigmented mole is an imperfect reproduction of a tactile organ. As a tactile organ it is abnormal in that the groups of tactile cells are embedded in the derma instead of being confined to the epidermis and the hair follicles, as is the rule in mammals, including man.

For all tumors there is a prototype, some normal tissue which the tumor reproduces more or less successfully. Pigmented moles in human beings occupy a peculiar position histologically in having no prototype in any mammalian skin. If, however, one looks at the creatures immediately below mammals in the phylogenetic scale, the reptiles and amphibia, one will see innumerable pigmented and elevated tactile spots with groups of innervated tactile cells in the derma forming tactile organs which bear a striking resemblance to human pigmented moles. Moreover, there is an evolutionary link between the tactile spot of the reptile and the human pigmented mole. This link is the evolution of mammalian hair.

The appearance of pigmented moles in the individual human skin today is explained by Lillie's views of embryonic segregation and the influence of environment, as shown by experimental embryology. The reptilian aspect of the pigmented mole places its origin at or before the reptilian stage of the human embryo. In or before this stage the cells destined to become hair follicles are pluripotential and may form either reptilian or mammalian tactile organs, for mammalian hair is a tactile organ. Some hereditary influence playing on the embryo or a slight change in environment induces certain cells to follow the reptilian pattern while most of the cells follow the normal pattern of hair follicles.

Chronologically, the appearance of pigmented moles at birth and shortly thereafter, the outburst of moles at puberty and their scanty scattering in after life parallel the formation of hair follicles in human skin. Another parallel is pigment formation. Of the various derivatives of the parent epidermis, pigment formation is constant and prominent only in hair bulbs and pigmented moles.

DISCUSSION

NATHAN CHANDLER FOOT: I should like to ask what results Dr. Laidlaw has obtained in the staining of the malignant melanomas by the Groz-Bielschowsky method; whether he finds any evidence of nerve terminals or nerve distribution in the malignant tumors. I have been unable to find nerve fibers in malignant melanomas, whereas in the benign type they are fairly easy to demonstrate in a rudimentary fashion with ordinary silver methods.

SAMUEL M. PECK: There are several points about the origin of nevus cells which still puzzle me, and I should like to have Dr. Laidlaw answer these questions. When one examines dozens of slides of pigmented nevi one gets the definite impression, except in rare instances, that the nevus cells originate from the ectodermal cells by "dropping." At least, this seems evident from ordinary hematoxylin-eosin preparations without any nerve stains such as Dr. Laidlaw has shown. Another point is that one does not see any mitotic figures in nevus cells, and therefore one must assume that in proliferation they arise either from the ectodermal structures or by amitotic division, which I cannot recall having seen. It is known that nevus cells often give a dopa reaction, and therefore they are melanoblasts. I think that no one has proved that nerve structures can build

pigment. How can these facts be explained in the light of what Dr. Laidlaw has brought out—that nevus cells in nearly all instances seem to arise from nerve structures?

GEORGE F. LAIDLAW: In answer to Dr. Foot's question, I have made no study of nerve fibers in malignant melanoma.

Dr. Peck brings up two interesting questions. Quite justly he asks the advocates of Masson's hypothesis to harmonize their views with Unna's well known *Abtropfung*, or the dropping down of epithelial cells from the epidermis into the derma to form nests of nevus cells. Secondly he questions the power of Schwann cells to form pigment.

As to the first point, in his original paper Masson himself pictures Unna's *Abtropfung* in full swing in the upper layers of a pigmented mole, while the nevus cells of the middle and lower layers seem to spring from nerve fibers or from their Schwann sheaths. This multiple origin of nevus cells has not received the attention which it deserves. Recognition of the multiple origin of nevus cells would settle many of the controversies over them. To this double origin as pictured by Masson, I should add a third, the endothelia of the lymph spaces, as first stated by von Recklinghausen. In his original monograph on neurofibroma, von Recklinghausen pictured cell nests of pigmented mole, and said that to his eye they looked like proliferating endothelia of the lymph spaces. To my eye, too, many nevus cells look so. While not enough is known about nevus cells to allow one to be dogmatic, a triple origin seems to be their best explanation.

As to the second point, the ability of Schwann cells to form pigment, I have studied many sections stained with silver and with the dopa reaction, but have never seen any evidence that the Schwann cell of the normal nerve fiber makes melanin. However, among neuropathologists it is well known that ganglion cells uniformly contain melanin, although I have never succeeded in getting a positive dopa reaction in them. In the embryo, the ganglion cell and the Schwann cell spring from the same mother cell, the neuroblast. The ganglion cell which remains in the nerve centers certainly makes melanin. The Schwann cells push out along the nerve fiber and proliferate there. Under normal conditions, they do not make melanin. Under pathologic conditions it is not improbable that the Schwann cells may retain or resume the melanin-making power of their parent cell, the neuroblast. Of course, this is pure hypothesis, unsupported by experiment.

NOTE.—Unknown to me, experimental confirmation of this hypothesis was already accumulating in the Osborn Zoological Laboratory, in New Haven, Conn., where Dushane had shown experimentally that in the amphibia the pigment cells of the skin spring from the neural crest. Mr. Dushane kindly permits me to refer to his work (Dushane, G. P.: Origin of Pigment Cells in Amphibia, *Science* **80**:620, 1934).

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Oct. 11, 1934

MORTON MCCUTCHEON, *President, in the Chair*

CHRONIC LYMPHATIC LEUKEMIA WITH PNEUMOCOCCIC MENINGITIS AND "PYEMIA." ROBERT W. MATHEWS.

A Negro, aged 49, was admitted to the Philadelphia General Hospital, to the service of Dr. Robert G. Torrey, with a history of sore throat for two months following electrodesiccation of the tonsils. One week prior to admission he had blurred vision. He had headache and stiff neck for three days, and was semistuporous for one day.

At examination the Negro was irrational and confused, crying out continuously. He presented a subconjunctival hemorrhage of the right eye, inequality of the

pupils, acute inflammation of the tonsillar fossae, marked cervical rigidity, a normal condition of the heart and lungs, a blood pressure of 120 systolic and 80 diastolic, and Kernig's sign bilaterally. The white blood cell count was 14,550, with neutrophils 5 per cent, lymphocytes 92 per cent and monocytes 3 per cent. The spinal fluid showed 60 cells, all of them neutrophils. A blood smear contained pneumococci of type III; a blood culture, pneumococci of the same type.

At autopsy the lungs showed passive congestion and septic infarction; the spleen, diffuse hyperplasia with splenomegaly. The kidneys were yellowish gray, of boggy consistency, with wedge-shaped, definitely demarcated, deep red areas at both poles and several circumscribed abscess cavities. The liver weighed 2,170 Gm. The parenchyma was firm, reddish brown, mottled by a yellow tissue which outlined the periportal network and central veins. The peripancreatic, renal and tracheobronchial lymph nodes were uniformly enlarged and whitish gray, and averaged from 2 to 4 mm. in diameter. The left sphenoid sinus contained purulent exudate. There was a localized suppurative meningitis of the frontal lobes.

Histologic examination showed diffuse lymphoid hyperplasia (small cell type) of the spleen and of the peripancreatic, renal and mediastinal nodes with loss of architecture, accompanied by leukemic infiltration of the kidneys, liver, bone marrow and brain. Septic infarcts were noted in the lungs and kidneys.

Clinically, with the blood picture, diagnosis presented three possibilities: meningitis with a leukemoid reaction, true leukemia complicated by meningitis, and subarachnoid hemorrhage as a feature of true leukemia. The report on the spinal fluid ruled out subarachnoid hemorrhage. A final diagnosis was impossible until autopsy. An interesting feature was the onset with sore throat and enlargement of the tonsils, the latter probably an expression of lympholeukemic hyperplasia in these structures. It is a matter of speculation whether the desiccated tonsils or the inflamed sphenoid sinus was the portal of entry for the pneumococci causing the meningitis.

ACUTE MONOCYTIC LEUKEMIA. PATRICK J. KENNEDY and EDWARD G. TORRANCE.

A white woman, single, aged 28, was hospitalized on Aug. 18, 1934. She was occupied as a bookkeeper until the onset, two weeks prior to examination, of weakness, dyspnea, vomiting after meals and pain in the upper left quadrant of the abdomen. The condition became progressively worse. There was no hemorrhage.

The patient was well developed, weighing 120 pounds (54.4 Kg.). She was conscious and cooperative. She was dyspneic, with an occasional dry cough, and had petechiae on the arms, chest and buccal mucosa. There were nodules in the submaxillary, cervical and supraclavicular regions. The thyroid gland was not palpated. There was hydrothorax on the left. A mass was felt in the upper part of the abdomen. The menses were present. The blood pressure was 118 systolic and 90 diastolic; the temperature, 99.2 F.; the pulse rate, 136; the respirations, 40. The hemoglobin content was 60; the erythrocytes numbered 3,000,000 and the leukocytes 105,000 per cubic millimeter. Differential smears contained large numbers of immature leukocytes. The bleeding time was 3.5 minutes; the coagulation time, 3.5 minutes; the platelets, 70,000. Albuminuria was present. The serologic findings were negative. The blood chemistry was normal.

On August 19, 1,000 cc. of hemorrhagic fluid was withdrawn from the left side of the chest. On August 20, the hemoglobin content was 45; the red blood cells numbered 2,220,000 and the white blood cells 115,100 per cubic millimeter. On August 21, treatment with x-rays, 92 roentgens, was given, and 500 cc. of hemorrhagic fluid was withdrawn from the left side of the chest. On August 23, the hemoglobin content was 38; the red blood cells numbered 1,444,000, and the white blood cells 26,000. On August 24, 450 cc. of whole blood was given. On August 25, the hemoglobin content was 40; the red blood cells numbered 1,670,000 and the white blood cells 19,150; 1,030 cc. of hemorrhagic fluid was taken from the left side of the chest. Vaginal bleeding began and increased daily. On August 29, the hemoglobin content was 25; the red blood cell count, 1,200,000; the white blood cell count, 64,800.

The abdominal pain increased. The patient retained no medicine given orally, became orthopneic and weaker, and died on August 29. An infiltrative tumor was found in the superior and anterior portions of the mediastinum. Other observations were: splenomegaly with multiple areas of necrosis; generalized enlargement of the lymph nodes; acute fibrinous pericarditis with effusion; healed mitral endocarditis; myocardial hypertrophy and degeneration; acute fibrinous pleuritis and hemothorax on the left side; collapse of the left lung; parenchymatous degeneration of the liver, and acute nephrosis of both kidneys.

The mediastinal mass consisted of round cells, fairly uniform in size and staining with a granular nucleus and pale cytoplasm. These were embedded in a thin fibrous tissue stroma. Capillaries were numerous, and some of the cells seemed to be proliferating from the capillary endothelium. Cells similar to these were present in the sinusoids of the liver, the sinuses of the spleen, the kidneys, lymph nodes and bone marrow.

ACUTE HEMOHISTIOBLASTIC LEUKEMIA. MAX M. STRUMIA.

A boy, aged 4½ years, was admitted to the Bryn Mawr Hospital on Feb. 23, 1934, in the service of Dr. J. McK. Mitchell. Five days prior to admission, the child had refused food and shown a rise in temperature. Later there were sweats and mild chills. On admission he appeared well nourished, had a cough, a purulent conjunctival exudate and an acute catarrhal infection of the nose and throat, with swollen, infected, ulcerated tonsils. The lungs showed evidence of consolidation over the left lower lobe and to a lesser degree over the right lower lobe. The diagnosis of pneumonia was made, and in the course of laboratory examination a most unexpected blood picture was found. The white cell count was 78,600 with a very large percentage of immature monocytic cells (monoblasts) and hemohistioblastic cells. There was also a very large number of immature and young granulocytic cells, probably representing an extreme type of reaction to the infection. The platelets were low (128,000), and the hemoglobin was below normal (10.44 Gm. in 100 cc.). The patient lived in the hospital for one week. During this time the white cell count increased gradually to 131,100, and the number of the monoblastic and hemohistioblastic cells greatly increased. The number of Rieder cells, as has been observed in other cases, also was high.

The terms "acute monoblastic leukemia" and "acute reticulo-endotheliosis" have no doubt been used synonymously for "acute hemohistioblastic leukemia." This name is used here to emphasize the type of cell prevailing, which, although bearing a strong resemblance to the monoblastic and monocytic types in general, still can be readily differentiated from them. The term "hemohistioblast" is used here in the sense of Ferrata, and the cell is very likely identical with the reticulo-endothelial cell of the fixed tissues.

VARIATIONS IN THE PATHOLOGIC MANIFESTATIONS OF LEUKEMIA. R. PHILIP CUSTER.

A brief analysis of the Philadelphia General Hospital series of cases of leukemia of all types is presented. The curve of incidence showed two peaks at the ages from 20 to 25 and from 40 to 45, with adjacent scattering through the ages from 5 to 25 and from 35 to 60, respectively. The shortest duration after the onset of symptoms was six days; the longest, five years. Particular emphasis is laid on the appearance of great numbers of megakaryocytes in the blood-forming organs of six patients with chronic leukemic myelosis, intimately associated with proliferating myeloblasts, each type of cell apparently bearing a genetic relationship to the general reticulum and sinus endothelium. Suggestive morphologic evidence that the so-called leukemic infiltrations are of autochthonous origin is presented. Photomicrographs of usual and unusual appearances in leukemic and aleukemic myelosis, lymphadenosis and reticulosis are shown, and rarefying bone lesions in the last named disease are demonstrated. Death from bilateral suprarenal necrosis due to arteriovenous thrombosis of suprarenal vessels is mentioned.

EXPERIMENTAL STUDIES ON LEUKEMIA. MAURICE N. RICHTER.

This is a review of the studies on mouse leukemia carried on in the department of genetics of the Carnegie Institution of Washington and the department of pathology of the College of Physicians and Surgeons, Columbia University. The data presented cover the following points:

1. The influence of heredity on the spontaneous occurrence of leukemia.

Leukemia occurred in about 90 per cent of mice over 6 months of age of the inbred strain C 58. Mice not having leukemia and those in which the diagnosis was doubtful had offspring with just as high an incidence of leukemia as did leukemic mice. The somatic condition of an animal at death (leukemic or non-leukemic) did not necessarily indicate its genetic constitution. The failure of leukemia to develop in 10 per cent of the mice was due to nongenetic factors.

In the inbred strain Storrs-Little, leukemia was very rare. In the F 1 generation from a cross of Storrs-Little and C 58 mice, the incidence of leukemia was about 50 per cent. As F 1 mice are genetically uniform, the operation of non-genetic factors is again evident, but to a different degree in these mice as compared with C 58.

In the generation from a back-cross to Storrs-Little, the incidence was about 25 per cent. Thus the incidence of leukemia in hybrids roughly paralleled the total heredity from the leukemic strain. A difference was observed in reciprocal matings, showing that one of the nongenetic factors involved was transmitted through the mother.

2. The influence of heredity on susceptibility to inoculation.

Any of the lymphatic leukemias arising in strain C 58 may be transmitted to normal mice of the same strain by inoculation of the latter with suspensions of leukemic cells. In other strains or in hybrids inoculation may or may not result in the transmission of leukemia. The results differ with different lines of leukemic cells and at different times, so that "susceptibility" and "resistance" are terms that can be used only with reference to specific cases. In a particular instance, the differential between strain C 58 and strain Storrs-Little with respect to inoculation with cells of line I was a single dominant gene.

3. The characteristics of leukemic cells.

In lymphatic leukemias of these mice, the cells are morphologically similar to normal lymphoid cells in certain stages of their development. In different transmission lines the cells have different cytologic features, with characteristic sizes, rates of division, rates of dispersion and sites of infiltration. In leukemias transmitted by inoculation, the cells of the infiltrations are direct descendants of the cells introduced. There are also metabolic changes which are characteristic for the particular line of leukemic cells. In a comparison of two particular lines, differences were observed in an increase of oxygen consumption or of glycolysis and the degrees to which the changes occurred.

Regular Meeting, Nov. 8, 1934

MORTON MCCUTCHEON, *President, in the Chair*

ARRHENOBLASTOMA OF THE OVARY (ADENOMA TUBULARE TESTICULARE): REPORT OF A CASE. MOSES BEHREND.

A woman, married, aged 50, was admitted to the Jewish Hospital, Jan. 28, 1934, for a large tumor in the right inguinal region. The mass had increased in size for three years. It was not painful to palpation or following exercise. For two years it was reducible, but in the year prior to examination it grew to a considerable size, became more uncomfortable and firmer, and was disfiguring and irreducible. There was no impulse on coughing. The patient was always in

excellent health; the heart and lungs showed no abnormalities. She never menstruated and never had any vaginal discharge. Sexual intercourse was indulged in with no lack of libido. Vaginal examination revealed a smooth mucous membrane, with absence of the cervix and uterus; the fallopian tubes and ovaries could not be palpated. She retained all outward physical womanly characteristics.

Operation was performed under spinal anesthesia. Through an incision in the right inguinal region a large solid mass presented itself seemingly attached to the broad ligament. The peritoneal cavity was then incised, and the tumor with its attachment to the broad ligament was removed. Before it was removed, however, a careful survey of the pelvis was made. The uterus, fallopian tubes and ovaries were absent.

Pathologic Report (Dr. S. Levine).—The tumor, elliptic in shape, weighed 1,030 Gm. and was very firm in consistency. On cross-section it was composed of dense grayish tissue. The central portion of the tumor was uniform in structure. Some sections were more hemorrhagic than others.

A section of the tissue was composed of a large number of cuboidal epithelial cells having an alveolar arrangement; the glands resembled seminiferous tubules. Many of them were arranged in cords. The epithelial cells centered about a lumen. The interglandular stroma contained a large amount of connective tissue and showed a moderate degree of hyalinization. Some of the folds presented infiltration by a solid cluster of cells. No ovarian elements were observed. This is a rare type of tumor. According to Pick, it is derived from the ovotestis; according to other authorities, it has its origin in the medullary cords which are the embryologic parent of both the ovary and the testis. Certain numbers of these tumors are associated with pseudohermaphroditism and hirsutism or infantile pelvic organs.

MELANOMA OF THE SKIN WITH UNUSUAL METASTASIS. BAXTER L. CRAWFORD.

[This case was reported in detail by Dr. Louis H. Clerf, under the title "Melanoma of a Bronchus; Metastasis Simulating Bronchogenic Neoplasm," in the *Annals of Otology, Rhinology and Laryngology* (**43**:887, 1934).]

The patient was a woman, white, aged 31. One and a half years after the removal of a pigmented mole from the upper part of the left arm by fulguration, a metastasis occurred in the main left bronchus, producing obstruction. This growth was repeatedly removed through the bronchoscope, the patient being symptom-free for intervals of several months each time. The patient died of a cerebral metastasis approximately one and a half years after the appearance of the bronchial metastasis and approximately three years after the removal of the melanoma from the arm.

SEBACEOUS HYPERPLASIA OF THE SKIN, INCLUDING SEBACEOUS ADENOMA; BEARING OF THE LATTER ON MULTIPLE ADENOMAS OF THE LIVER. ROBERT L. GILMAN and FRED D. WEIDMAN.

Three types of sebaceous hyperplasia are indicated: (1) a true inflammatory adenomatous hyperplasia such as is seen in rhinophyma; (2) a noninflammatory sebaceous hyperplasia probably due to Demodex, and (3) a sebaceous nevus. A number of parallelisms are cited between the latter and multiple adenomas of the liver, which may point to a nevic (congenital) basis, also, for what have hitherto been classified as multiple adenomas of the liver. The points in common are: the multiplicity of the lesions, their dissemination throughout the organ, their uniform size, the absence of ulceration or tendency to carcinomatous change, the absence of encapsulation and the embryonal cytology.

The opportunity is also taken to compare the cytologic features of adenomatous hyperplasias around foci of Clonorchis sinensis infestment of the liver, on the one hand, with those of noninflammatory (supposedly demodectic) sebaceous hyperplasias on the other. It is concluded that as the two are of the same order, the "embryonal" features of the latter should not be invoked to force it into the category of nevi. It can still qualify as an adenomatous (but noninflammatory) hyperplasia.

THE INCIDENCE OF MALIGNANT TUMORS AT THE PHILADELPHIA GENERAL HOSPITAL FROM 1867 TO 1933, WITH ESPECIAL REFERENCE TO PRIMARY CARCINOMA OF THE LUNG. HERBERT LUND.

The records of autopsies at the Philadelphia General Hospital from 1867 to 1933 were surveyed by paging through the protocols. Each instance of a malignant tumor was noted, and the following data were obtained: serial number, type of tumor, location of primary growth, presence of metastasis and extension, microscopic diagnosis, agreement or disagreement between gross and microscopic diagnosis, agreement or disagreement between clinical and pathologic diagnosis, age of subject, whether or not the patient was treated at the tumor clinic, and, in cases of primary tumor of the lung, sex and color. Protocols of postmortem examinations were reviewed to the number of 26,700. Those that did not contain descriptions of at least the thoracic and abdominal viscera were omitted. The cases were classified according to the location of the lesion rather than its type. It was found that in the early records tumors with descriptions suggesting a benign growth were often diagnosed as sarcoma, hypernephroma or even carcinoma. This produced a margin of error. An attempt has been made to evaluate it. In certain instances the description was not clear as to the primary source of the tumor, and in these instances the tumor has been classed as one of unknown origin. All the available slides or microscopic sections of primary tumors of the lung, tumors of unknown origin in which the lung was involved, mediastinal tumors and growths in which malignancy was doubted were reviewed. The changing facilities for the diagnosis and treatment of tumors at the hospital and the changing accommodations for all types of cases were noted.

It was found that the incidence of malignant tumors in general had more than doubled in the period covered by the survey. The major increases were at 1900, 1920 and 1922. There was a moderate drop after 1924. Not all tumors had a similar increase. Little increase was shown by tumors of the stomach, pancreas, rectum, liver, kidney, gallbladder and bile ducts, bone, suprarenal gland, retroperitoneal region, duodenum and ampulla and by tumors of miscellaneous and unknown origins. Mediastinal tumors decreased in number at 1910, and at the time of the survey (1933) there were no tumors with such a diagnosis. Tumors of the brain and cord were almost always benign and were not included in the survey except for their incidence. Their number had not increased. Hodgkin's disease was studied as a side issue. Its incidence increased at 1910 but did not change much after that. The tumors that increased in number included those of the uterus, breast, skin, oral cavity, colon, esophagus, prostate, lung, bronchus and trachea, bladder, larynx, ovary, vulva and vagina, penis, testis, lymph nodes, spleen and thymus, small intestine and thyroid gland. Those of the uterus, breast, skin and oral cavity showed the greatest quantitative increase. Those of the uterus, skin, oral cavity, prostate, lung, bronchus and trachea, bladder and larynx showed the greatest relative increase. The "external" lesions (uterus, breast, skin, oral cavity, vulva and vagina, penis and testis) showed their major increases at 1920 and 1922. The major increase of tumors of the colon, lymph node, spleen, thymus, prostate, lung, bronchus and trachea was at 1920. The major increase of tumors of the bladder and larynx was at 1922. The major increase of tumors of the ovary was at 1924. Tumors of the small intestine and thyroid gland were so few and scattered that it was difficult to draw any conclusion.

The ages of bodies subjected to postmortem examination are higher now, on the average, than formerly. Before 1900 the greatest number of deaths occurred between 25 and 55 years of age. The peak of deaths at present is between 40 and 70 years of age. This, no doubt, explains a moderate increase of all types of tumors, especially those more characteristic of old age, such as carcinoma of the esophagus, skin and oral cavity. The greatest number of deaths from malignant disease was between the ages 45 and 70 throughout the span of the study.

The death incidence by wards of the hospital changed. Before 1890 there was a much larger percentage of deaths in the children's ward, mostly those of foundlings, and in the obstetric ward. Deaths from tuberculosis stayed at about

the same number. Deaths in the other wards, such as the surgical, neurologic and medical wards, increased moderately.

The hospital purchased its first x-ray equipment about 1900. In 1922 it made a large purchase of radium and instituted what is called the "radium clinic." Easily diagnosed tumors such as those of the breast, skin, oral cavity, uterus, etc., make up the greater number of tumors handled by this clinic. The clinic, no doubt, contributed to the increase in the figures for such tumors.

Less than 1 per cent of the autopsies included microscopic examinations before 1900. Between 1900 and 1920 this percentage increased to about 35. In 1920 a new laboratory building was erected, the laboratory force was increased, and well over 90 per cent of all autopsies after that time included microscopic examinations. The sharp increase after 1920 of many types of tumors is probably explained by this factor. Gross diagnosis was accurate in regard to most tumors (in from 90 to 100 per cent of cases). There was from 85 to 90 per cent agreement between the gross and microscopic diagnoses in regard to tumors of the gallbladder, bile ducts, liver, kidney and lymph nodes. There was from 80 to 85 per cent agreement in regard to tumors of the prostate and tumors of unknown origin, from 70 to 75 per cent agreement in respect to duodenal and pulmonary tumors, and only from 0 to 10 per cent agreement in regard to tumors of the small intestine. One would expect, therefore, that with the institution of routine microscopic examinations there should have been an increase in the number of tumors which are not easily diagnosed grossly.

Improvement in clinical diagnosis may have been a factor. There was little change in regard to external lesions, but there was a definite improvement in the diagnosis of tumors of the internal organs. In regard to tumors of the stomach, colon, rectum, prostate, ovary, thyroid gland, larynx, esophagus, bone, retroperitoneal region and miscellaneous sites, 40 per cent were accurately diagnosed clinically before 1920. At the time of the survey (1933) 64 per cent were correctly diagnosed clinically. In regard to tumors of the lung, bronchus and trachea, liver, gallbladder, pancreas, kidney, suprarenal gland, lymph nodes, small intestine, duodenum and mediastinum, 25 per cent were correctly diagnosed before 1920 and 32 per cent at the time of the survey. Tumors of the lung, bronchus and trachea were correctly diagnosed before 1920 in none of the cases. At the time of the survey these conditions are correctly diagnosed in 39.2 per cent of the cases.

The attitude of pathologists changed. This was demonstrated by a review of 15 cases of so-called endothelioma of the lung and pleura. The tumors were presented to 4 prominent pathologists (Joseph McFarland, B. L. Crawford, J. H. Clark and R. P. Custer). Not one agreed that the diagnosis should be endothelioma. Among these tumors many primary carcinomas of the lung were found. Other diagnoses were: metastatic carcinoma or sarcoma, carcinoma of unknown origin, and even Hodgkin's disease. Five cases of sarcoma of the lung or pleura were also reviewed; 2 cases of primary carcinoma of the lung were found. Five instances of so-called mediastinal tumor were reviewed; 3 cases of primary tumors of the lung were found. Pathologists at present look for tumors of the lung and bronchus, which formerly were disregarded. The same statement is true, to a certain extent, of tumors of the prostate.

There are arguments for an actual increase of primary carcinoma of the lung. The increase is so marked that it cannot be attributed to the changing attitude of pathologists: In the period reviewed the incidence changed from 0.02 per cent in persons examined post mortem to 0.58 per cent. The position of carcinoma of the lung in relation to other tumors in regard to incidence changed from that of twenty-third to sixth; it was preceded only by tumors of the stomach, uterus, breast, colon and prostate. There has been a moderate increase since 1922, in a period during which the modifying factors have remained the same.

There are arguments against an actual increase of primary carcinoma of the lung. The changes of incidence seem to coincide with the increase in the percentage of microscopic investigations. The moderate increase since 1922 may be due to improved clinical diagnosis and the changing attitude of the pathologist toward the frequency of such carcinoma.

ISSUES AT STAKE IN GRADING OF TUMORS. STANLEY P. REIMANN and CLARK E. BROWN.

The authors graded 173 cases of carcinoma of the breast on which they had adequate follow-up data over a period of five years. An appraisal of clinical and histologic methods was made, and an unsuccessful attempt at combining them was made.

The results of histologic grading were as follows:

Grade	Cases	Patients Who Survived 5 Years	Percentage
I	30	22	73
II	109	26	24
III	34	2	6

The results of the combined histologic and clinical methods were as follows:

Grade	Cases	Patients Who Survived 5 Years	Percentage
I	11	11	100
II	162	39	24

The period of delay before operation was offered as one explanation for the failure of histologic criteria, since the average period of delay in grade I survivals was eleven months, while that for grade I deaths was sixteen months. In the more malignant grades no such explanation was applicable, and failures of prognosis were laid to pure chance.

It was concluded that in the individual case, histologic and clinical prognosis finds accurate use in only a highly limited number of cases. General support to Hansemann's theory that the more anaplastic the cells of a tumor, the greater is its tendency to metastasize and recur was pointed out.

CHICAGO PATHOLOGICAL SOCIETY

I. PILOT, M.D., *President, in the Chair*

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EDWIN F. HIRSCH, M.D., *Secretary*

THE RABBIT LUNG AFTER PHRENICOTOMY AND PNEUMOTHORAX. C. G. LOOSLI.

Rabbit lungs which had been made atelectatic by phrenicotomy and pneumothorax were kept in a state of collapse for from one to forty days. The lungs were fixed in Zenker's fluid to which dilute solution of formaldehyde had been added, and were then embedded in pyroxylin, sectioned and stained to show collagenous, reticular and elastic fibers and cellular details.

In the completely collapsed lung the lumens of the alveolar ducts, alveolar sacs and alveoli were present as narrow, branching clefts. At the junction of the terminal and respiratory bronchioles with the alveolar ducts, the bronchial epithelium and its basement membrane ceased abruptly, while the connective tissue and blood vessels of the lamina propria continued on and formed the walls of the alveolar ducts and alveoli. The free surfaces of the alveolar ducts between the mouths of adjoining alveoli were covered with capillary loops which continued onto the alveolar septums.

Each alveolar septum contained a network of capillaries which coursed back and forth from one side of the septum to the other. The reticular and elastic fiber network, in and on which the capillaries rested, was separated from the alveolar spaces by bulging capillary loops. The septal cells did not form a continuous membrane over the capillary loops in the alveolar septums following collapse of

the lung but remained in the intercapillary spaces, intimately associated with the connective tissue as isolated cells. Thus a continuous histologic epithelium was not found lining the alveolar ducts and alveoli in the completely collapsed lung.

DISCUSSION

W. BLOOM: These experiments show that the alveolar epithelium which lines the embryologic lung ceases to exist at birth.

ADAMANTINOMA WITH ORIGIN FROM THE HYPOPHYSEAL DUCT. H. ZEITLIN.

The clinical and anatomic findings in three cases of adamantinoma with origin from the hypophyseal duct are reported. The first case was that of a white girl, aged 3, who complained of rapidly progressing impairment of vision and tottering gait. The child also had a complete change of personality. Her previous history was that of a normal child.

Roentgenograms revealed a suprasellar calcification with marked enlargement of the sella turcica, separation of the cranial sutures and mild hydrocephalus.

After surgical intervention, the child contracted scarlet fever and died. Necropsy revealed an irregular cystic tumor in the region of the infundibulum. The microscopic diagnosis was that of a suprasellar cystic adamantinoma with atypical enamel formation.

The second case was that a Chinese man, aged 40, who died following severe uncontrollable epistaxis. Necropsy disclosed an intrasphenoid squamous cell carcinoma of adamantinoma type (hypophyseal duct carcinoma of Erdheim) which had arisen from within the body of the sphenoid bone, filled the sphenoid sinus, extended into the posterior part of the roof of the left orbit, the left middle ear and the right internal jugular vein, invaded the posterior lobe of the hypophysis and eroded through the dura with local metastasis to the infundibulum. Histologically the tumor was formed of alveoli embedded in much stroma composed of dense fibrillary connective tissue. The alveoli consisted of two types of cells: cylindric and cuboid cells at the periphery, and in the center stellate cells with slender protoplasmic bridges forming a loose network. The tumor was an adamantimona rather than a squamous cell carcinoma. There was no evidence of anaplastic changes or mitosis. The malignant character was manifested in the manner of growth and spread rather than in the microscopic appearance of the cells.

The third case was one of benign intracystic papillary adamantinoma. Interlacing epithelial columns lined by a single row of cuboid cells, central masses of stellate cells with a tendency to whorl formation, calcareous deposits and numerous cysts further determined the character of this tumor.

DISCUSSION

I. PILOT: Apparently these adamantine tumors can attain considerable size as compared with those in the jaw.

RUPTURE OF AORTIC ANEURYSM INTO THE PULMONARY ARTERY. D. L. POTTER.

Rupture of an aortic aneurysm into the pulmonary artery is an unusual accident. About 54 accounts have been published.

Among 1,727 autopsies at St. Luke's Hospital, there were only 6 thoracic aneurysms, an incidence of 0.35 per cent. Of these, 3 had ruptured, one into the superior vena cava, another into the left lung, and the third into the pulmonary artery.

A white man, aged 53, entered St. Luke's Hospital on June 11, 1933, at 10 p. m., under the care of Dr. Carl Rinder, with a history of precordial pain of twenty-four hours' duration which had followed strenuous exertion, marked dyspnea and palpitation. The pain was persistent, acute, stabbing, and did not radiate, and was not relieved by morphine. The patient was acutely ill when admitted. His blood pressure was 72 systolic and 48 diastolic. There was a loud blowing systolic murmur at the base and apex of the heart; the skin was cold and moist;

the lips were moderately cyanotic; there were signs of pulmonary edema. Despite stimulation, the condition remained unchanged, and the patient died four hours after admission to the hospital and fifty-one hours after the onset of the severe symptoms. The clinical diagnosis was coronary thrombosis. Dr. Edwin F. Hirsch did the autopsy eight hours after death. The essentials of the anatomic diagnosis were: sacculated aneurysm of the aortic arch ruptured in the pulmonary artery; marked syphilitic sclerosis with fatty changes of the aorta, and marked passive hyperemia and edema of the lungs.

There was a sacculated aneurysm in the ascending and transverse portions of the aortic arch, 7.5 cm. in diameter. Marked syphilitic and fatty changes involved 75 per cent of the lining of the thoracic portion of the aorta. The ascending and transverse portions of the aorta were dilated, and at the origin of the innominate artery the inside diameter was 12.5 cm. Just below this on the left side was a saccular dilatation with a hiatus 5.5 cm. in diameter, which bulged from 3 to 4 cm. In the base of the aneurysm was a slit 1.2 cm. long that opened into the pulmonary artery 4 cm. distal to the pulmonic leaflets. The sac was lined by a thin layer of closely adherent fibrin. A Kahn test made with blood serum obtained post mortem was 100 per cent positive.

Focally in the media and adventitia of the aorta were dense collections of lymphocytes, plasma cells and fibroblast tissues. These were distributed about the vasa vasorum, and many were 0.5 mm. in diameter. Along the periphery were small infiltrations of polymorphonuclear leukocytes. Many of the alveoli of the lungs contained red blood cells, and the blood vessels, even the capillaries, were markedly dilated. There was marked chronic passive hyperemia of the liver. Because of the anatomic structure of the aneurysm, the histologic changes in the wall of the aorta and the serologic reaction for syphilis, there is no other conclusion but that the aneurysm of the aorta was syphilitic.

Summary.—Approximately 55 aneurysms that ruptured into the pulmonary artery, including the one described here, have been reported since Well's original description in 1812.

An acute attack of dyspnea, severe pain in the chest, coughing, vomiting and subsequent edema of the lower extremities, associated with a loud systolic murmur in the left second and third interspaces and a marked thrill over the base of the heart and to the left of the sternum, are the characteristic symptoms of this vascular disorder.

An aortic aneurysm rupturing into the pulmonary artery is usually small, and arises in the ascending portion or first portion of the transverse part of the aorta. Syphilitic sclerosis of the aortic wall is the usual etiologic factor.

DISCUSSION

S. LEVINSON: The incidence of aneurysm of the ascending portion and arch of the aorta apparently is greater in the Cook County Hospital than in St. Luke's Hospital.

MYOSARCOMA OF THE DIAPHRAGM. J. D. KIRSHBAUM.

A careful search of the literature disclosed only 6 cases of primary tumor of the diaphragm. Three of the tumors were malignant, 2 of them myogenous. In a series of 6,250 autopsies at the Cook County Hospital since 1929, 2 primary malignant tumors of the diaphragm were seen.

The first case was that of a white man, aged 47, with symptoms of three and one-half months' duration. At autopsy a mass 14 by 12 by 10 cm. was located on the right pleural surface of the diaphragm, and a smaller mass, 11 by 6 by 9 cm. in diameter, on the left side. The tumor was moderately firm, meatlike and light grayish white. Both lungs had many gray-white nodes up to 30 mm in diameter.

The tumor was composed of long band-shaped cells with large and bizarre-shaped nuclei. Many of the nuclei were lobulated. In the cytoplasm of some of the cells there were fine deep blue granules, which varied in number and tended

to be arranged in longitudinal rows, best seen with Mallory's phosphotungstic acid-hematoxylin stain. The microscopic appearance of the tumor suggested a very undifferentiated, undeveloped striated muscle cell tumor without cross-striations, a myoblastic sarcoma of the diaphragm.

The second case was that of a white man, aged 58, with symptoms of four months' duration. At autopsy a firm gray-white tumor, 18 by 16 by 13 cm., was found on the pleural surface of the left side of the diaphragm and attached to the inner side of the left lower margin of the sternum and ribs. There were metastases to the pleura, liver and lung.

The tumor was cellular, composed of spindle-shaped cells, with irregular hyperchromatic nuclei. In places the cells were arranged in parallel bundles. Mitotic figures were numerous. Intracellular fibrils were seen with Mallory's special stain for muscle cells. Leiomyosarcoma of the left side of the diaphragm was diagnosed.

The diagnosis in such cases is practically never made clinically. In both patients the course was rapid, death occurring in less than four months. The pleural surface of the diaphragm was affected in both.

Tumors derived from striated muscle fibers may be divided into two groups. Tumors of the first group are composed of undeveloped, immature skeletal muscle cells and are either benign (myoblastic myoma, described by Abrikossoff and R. Meyer) or malignant (myoblastic sarcoma). The benign tumors have large polyhedral cells with small central round nuclei and pale-staining ample cytoplasm containing fine granules arranged in rows. These tumors are circumscribed and do not recur when removed. The malignant tumors show cellular pleomorphism, with syncytial-like cells containing ample cytoplasm. Rows of granules appear in the cytoplasm and are the analogues of the myofibrils. The first tumor described in this report suggested a myoblastic origin.

Tumors of the second group are derived from developed, more mature striated muscle fibers, which may have lost their differentiation. Cross-striations may or may not be present. These are either benign (rhabdomyoma) or malignant (rhabdomyosarcoma).

The two growths described illustrate two types of undifferentiated mesenchymatous tumors of the diaphragm, which appeared to be myogenic in origin.

DISCUSSION

W. Bloom: Intracellular fibrils are neither reliable nor specific criteria for recognizing smooth muscle cells.

I. Pilot: I have studied pleural tumors of the lungs with essentially the same structure of tissue as this leiomyosarcoma. Some have been benign and were diagnosed as fibromyoma.

E. F. Hirsch: The tissue pattern of the tumor diagnosed as rhabdomyosarcoma repeats in many ways that of a mesoblastic sarcoma not necessarily originating in skeletal muscle. In a reported case of rhabdomyosarcoma (Hirsch, Edwin F.: Arch. Path. 8:9, 1929) there were many spindle cells with cross-striations. I think that if the first tumor arose in skeletal muscle it would have some cells with cross-striations.

Book Reviews

Physiologie et physiopathologie du système réticulo-endothélial. By Albert H. Du Bois, Chef de clinique nationale Universitaire de Génève. Préface du Professeur M. Roch. Price, 36 francs. Pp. 204. Paris: Masson et Cie, 1934.

This book gives a review of the reticulo-endothelial system under normal and pathologic conditions. The first part deals with the experimental physiology of the system under the following headings: morphology, vital staining (colloid pexis), blockade, relations to blood cells and arachnoid fluid and functional tests. The second part reviews the relations of the system to normal and pathologic processes. There are chapters on the rôle of the system in the metabolism of physiologic pigments, of lipids, of carbohydrates, of water and of proteinic substances and chapters on the system in infectious diseases, intoxication and experimental malignant tumors. The third part discusses the reticulo-endothelial system in therapy, with reference particularly to internal secretions, the roentgen rays and chemotherapy. It is emphasized that the study of the reticulo-endothelial system may be regarded as an introduction to the study of the physiology of connective tissue. There is an extensive bibliography of no less than thirty pages. The review will be of value to all who may be interested in the reticulo-endothelial system.

Books Received

PHYSICAL CHEMISTRY FOR STUDENTS OF BIOLOGY AND MEDICINE. David Ingersoll Hitchcock, Ph.D., Associate Professor of Physiology in the Yale University School of Medicine. Edition 2, with laboratory directions. Price, $2.75. Pp. 214, with 27 illustrations. Springfield, Ill.: Charles C. Thomas, publisher, 1934.

THE BRAIN AS AN ORGAN: ITS POSTMORTEM STUDY AND INTERPRETATION. Frederic and Florence Wertham. With an introduction by Adolf Meyer, M.D., Johns Hopkins Hospital. Price, $7.50. Pp. 538, with over 160 illustrations. New York: The Macmillan Company, 1934.

RECHERCHES EXPERIMENTALES SUR QUELQUES ESTERS DE LA CHOLINE. Maurice Villaret, L. Justin-Besançon and René Cachera. Price, 38 francs. Pp. 254, with 79 illustrations. Paris: Masson et Cie, 1934.

LA PROTIDÉMIE ET LA PRESSION OSMOTIQUE DES PROTIDES: RECHERCHES EXPÉRIMENTALES ET APPLICATIONS CLINIQUES. Antoine Codounis, Professeur agrégé à la faculté de médecine d'Athènes. Préface du Professeur C. Achard. Price, 36 francs. Pp. 212. Paris: Masson et Cie, 1934.

PHYSIOLOGIE ET PHYSIOPATHOLOGIE DU SYSTÈME RÉTICULO-ENDOTHÉLIAL. Albert H. Du Bois, Chef de clinique nationale universitaire de Génève. Préface du Professeur M. Roch. Price, 36 francs. Pp. 204. Paris: Masson et Cie, 1934.

THE PATIENT AND THE WEATHER. VOLUME II. AUTONOMIC DISINTEGRATION. Willam F. Petersen, M.D., with the assistance of Margaret E. Milliken, S.M. Pp. 530, with 249 figures. Volume III. MENTAL AND NERVOUS DISEASES. Price, each $5. Pp. 375, with 192 figures. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934.